

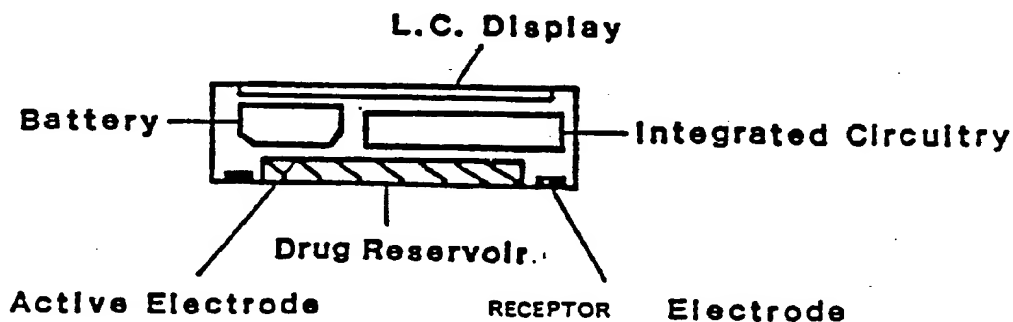


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: <b>PCT/US92/07221</b> (22) International Filing Date: <b>26 August 1992 (26.08.92)</b>  (30) Priority data: 749,928                      26 August 1991 (26.08.91) <b>US</b>  (71) Applicant: <b>RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY [US/US]; Old Queens Building, Somerset And George Streets, New Brunswick, NJ 08903 (US).</b> (72) Inventors: <b>CHIEN, Yie, W. ; 5 West Lake Court, North Brunswick, NJ 08902 (US). SHI, Wei-Min ; 81 Lincoln Avenue, Piscataway, NJ 08854 (US).</b>		(74) Agent: <b>SINN, Leroy, G.; P.O. Box 559, Oldwick, NJ 08858 (US).</b>  (81) Designated States: <b>AU, CA, DK, ES, FI, JP, KR, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).</b>  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: IONTOTHERAPEUTIC DEVICE AND PROCESS

# TRANSDERMAL PERIODIC IONTO-THERAPEUTIC SYSTEM ( TPIS )



## (57) Abstract

This invention relates to a portable, lightweight iontotherapeutic device for regulated transdermal systemic administration of ionizable pharmaceutical compounds. The device has a preprogrammable control element which controls the iontotherapeutic administration in accordance with a prescription and other instructions entered into the control element by interface with a computer system and which can communicate data on the iontotherapy by interface with a computer system. It also provides an iontotherapeutic process for automated transdermal administration of ionized pharmaceuticals by use of the device. Also provided is a novel battery belt adaptable for use with the device.

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## IONTOTHERAPEUTIC DEVICE AND PROCESS

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CROSS-REFERENCE TO RELATED APPLICATION

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This application is a continuation-in-part of U.S. Application Serial No. 07/587,406 filed September 25, 1990 and of U.S. Application Serial No. 07/046,984, filed May 5, 1987, now U.S. Patent No. 5,042,975, which was a continuation-in-part of U.S. Application Serial No. 890,702 filed July 25, 1986, now abandoned.

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TECHNICAL FIELD

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This invention relates to development of an iontotherapeutic device for regulated transdermal systemic administration of ionizable pharmaceuticals (including ionizable biopharmaceuticals) and a novel battery device usable as an element of said device.

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It also provides an iontotherapeutic process for transdermal administration of ionizable pharmaceuticals, particularly those which are otherwise transdermally absorbed to a small degree or not at all. The invention also relates to a polymeric unit dose in which an ionized pharmaceutical is dispersed. The unit dose is adapted to be assembled as a part of either the anode or the cathode, depending upon whether the ionized pharmaceutical is cationic or anionic, so that the ionized pharmaceutical will be delivered transdermally and then be absorbed systemically when the iontotherapeutic device is in operation.

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BACKGROUND ART

10 Many pharmaceuticals are required to be administered to  
patients by injection. A notable example is insulin, which  
cannot be administered orally to be effective in lowering  
15 the elevated blood sugar levels, which are too high in  
diabetics (i.e., > 126 mg/dL). Other pharmaceuticals may be  
administered orally, but in some cases, there is inefficient  
20 absorption into the bloodstream to permit the pharmaceu-  
ticals to achieve their intended therapy. Also, with regard  
to oral administration, many orally administered pharmaceu-  
25 ticals undergo a high degree of destruction by the hepato-  
gastrointestinal first-pass metabolism. Often the metabo-  
lites of the first-pass metabolism cause unwanted biological  
30 activity or toxicity. In oral administration, there are  
variables which cause undesirable variations in the extent  
35 of gastrointestinal absorption from subject to subject,  
especially in the case of some pharmaceuticals; and there  
are also associated problems of uneven blood levels result-  
40 ing from an initial large absorption with attendant un-  
desirable side effects or toxicities, and subsequent blood  
45 levels which are less than therapeutically optimal.

50 Recently there has been an increasing interest in  
transdermal delivery. However, it is desired that transder-  
mal absorption of a number of pharmaceuticals, particularly  
the macromolecular drugs such as insulin and cationic drugs  
55 like propranolol HCl, be improved.

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The hazard and discomfort of administration of pharmaceuticals by injection, especially if therapy is required on a frequent basis, such as the subcutaneous injection of insulin for diabetes therapy, which is required daily, are universally known. There has long been a desire to avoid the necessity of therapy by injection.

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Investigations have been carried out to explore the possibility of delivering certain therapeutic agents topically by use of a direct current (DC) iontophoresis. For example, it has been found that fluoride ions can be assimilated into the structure of a tooth with the aid of DC iontophoresis. Also, localized "seating" has been caused by delivering to the skin a sweat-inducing compound, such as pilocarpine, using a direct current. The induced sweat is then assayed using an electrode to determine its chloride ion concentration for diagnosis purposes. A low chloride content in the sweat indicates that a patient may be suffering from cystic fibrosis. Application of a DC iontophoresis can be uncomfortable particularly when the level of applied current is at a high level, in the case of certain pharmaceuticals, in order to achieve a systemic therapeutic level.

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It is highly desired to provide improved iontotherapeutic devices and processes and unit dose forms for use therein and to provide further thereby therapeutic levels of systemically-effective pharmaceuticals efficiently with a physiologically-acceptable low electric current.

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SUMMARY OF THE INVENTION

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A process has been found for administering transdermally a systemically effective amount of an ionizable pharmaceutical in sterile aqueous solution using an iontotherapeutic device such as provided by this invention. The ionized pharmaceutical solution can be contained in a unit dose form such as disposable polymeric matrix unit dose form in which a dosage amount of an ionized pharmaceutical solution (pH desirably at least about 1.0, 1.5 or about 2 pH units above or below the pKa or isoelectric pH of the ionizable pharmaceutical) is intermixed with a polymer which is characterized by being compatible with the pharmaceutical as well as the skin, hydrophilic, and capable of releasing the pharmaceutical for iontotherapeutic transdermal absorption. The unit dose form can also comprise a sterile solution of the ionized pharmaceutical contained within a closed reservoir unit dose form having a drug-releasing microporous membrane surface. The unit dose forms are assembled with a pharmaceutical reservoir electrode and are further adapted to permit the dissolved, ionized pharmaceutical to be delivered iontophoretically to the skin of the subject treated and to provide iontotherapeutic transdermal absorption of a systemically effective amount of the pharmaceutical. The unit dose forms are maintained covered to retain sterility until the desired time of iontotherapeutic administration. A pharmaceutical reservoir electrode which will receive such a unit dose form is used as a part of the

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iontotherapeutic device, such as provided by this invention, which is used to carry out the iontotherapeutic delivery and transdermal absorption of the ionized pharmaceutical. The pharmaceutical reservoir electrode is either a cathode or an anode depending upon whether the pharmaceutical is in anionic or cationic form, respectively. The iontotherapeutic device provides, in the process, an iontotherapeutically effective and physiologically acceptable pulse current with a specific waveform having an amplitude such as up to about 10mA based on a reservoir electrode skin-contacting area of about 5 cm<sup>2</sup> and an effective frequency of at least about 10 Hz up to about 50 KHz until the subject treated has received a pharmacologically-effective systemic dosage of the ionized pharmaceutical.

The pharmaceutical administered by this invention can be selected from pharmaceuticals which ordinarily are not transdermally absorbed through intact skin in an effective dosage amount, such pharmaceuticals including but not limited to insulins, vasopressin, heparin, growth hormones, glucagon, oxytocin, and other macromolecular drugs as well as a number of others which can be provided in ionized form. A number of compounds which are naturally-occurring in humans, or variants thereof, and which often are peptide in nature, are also included within this pharmaceutical group, many of which can be produced identically or as a related

5 compound using DNA recombinant or other biological techniques.

10 Also provided by the invention is a novel iontotherapeutic device capable of transdermally administering a systemically effective amount of an ionized pharmaceutical.  
15 The device is a lightweight, portable transdermal periodic iontotherapeutic device for transdermal administration of a  
20 systemically-effective amount of an ionized pharmaceutical, which is adapted to be worn by a subject being iontotherapeutically treated, comprising

- 25 1) a DC power supply capable of providing an iontotherapeutically effective and physiologically acceptable DC  
30 current in the range up to about 10mA;
- 35 2) a periodic waveform generator electrically connected to the DC power supply and having integrated circuitry capable of providing a) a periodic waveform in the  
40 square, triangular, sinusoidal, trapezoidal, or other acceptable geometric form or combination thereof; b) an on/off ratio of 1/50 to 10/1; and c) a repetition frequency from about 10 Hz to about 50 KHz;
- 45 3) an output circuit electrically connected to said waveform generator which a) can provide a periodic DC current in a pre-selected waveform of said forms; b) monitors current intensity delivered; c) adjusts and maintains the current intensity within predetermined maximum and minimum levels and d) delivers the current to a  
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reservoir electrode for iontotherapeutic transdermal administration of said ionized pharmaceutical;

- 4) a pharmaceutical reservoir electrode which can be pre-selected to be either the cathode or the anode depending upon whether the ionized pharmaceutical is anionic or cationic; said electrode having a receptacle adapted to receive a unit dose of said ionized pharmaceutical in which said ionized pharmaceutical is in aqueous solution at a pH at least 1.0 pH unit below or above the isoelectric point or pKa point of said ionized pharmaceutical ; said electrode with said received unit dose adapted to be placed in electrical contact with the intact skin to be treated iontotherapeutically; said electrode having a terminal to receive and to transmit through said unit dose the said periodic DC current and said unit dose adapted to be in electrical contact with said terminal;

- 5) receptor electrode adapted to be in electrical contact with the intact skin to be treated and forming with said pharmaceutical reservoir electrode a combination of anode and cathode electrodes;

said electrodes electrically connected to said output circuit and providing when placed upon the skin of a subject being treated a current path through the intervening tissue of the subject being treated; and

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6) a preprogramable control element electrically integrated within said device to preprogram and to control said iontotherapeutic administration on an automated basis as in accordance with a physician's prescription entered into the control element, without interaction of a subject being treated with the device for said administration except to permit said subject to stop operation of the device as in the event of an emergency.

The device will ordinarily have a terminal by which the transdermal administration carried on by the device can be monitored using a computer system and a connecting line to connect the device and the computer system or by which a prescription for administration of a pharmaceutical by the device can be entered into the programmable control element by use of a computer system and a connecting line to connect the control element with the computer system.

Further, the device desirably has one or more additional terminals by which the control element can be connected by a connecting line with a sensor to sense a skin condition or with a separate sensor to sense a level of an entity in the body (which correlates with a need for administration of the pharmaceutical), the sensor(s) held in intimate contact with the subject's body and signals said control element on need for administration or skin condi-

5           tion. For example, in insulin iontotherapy, the signal can  
transmit the nature of need for insulin administration.

10           Further, the invention provides a process for adminis-  
tering an ionized pharmaceutical by use of the above defined  
15           device and carrying out the following steps:

- 20           1) entering a prescription or other instructions into the  
control element of said device using a computer system;
- 25           2) assembling a dosage unit containing a pharmaceutically  
acceptable aqueous solution of said peptide into a  
30           receptacle of a reservoir electrode of a transdermal  
periodic iontotherapeutic system, which electrode is a  
cathode or anode depending upon whether such ionized  
35           peptide is anionic or cationic, said solution having a  
pH at least about 1.0 pH unit below or above the iso-  
electric point of said peptide;
- 40           3) placing the cathode and anode electrodes of said trans-  
dermal periodic iontotherapeutic system in electrical  
contact with the intact skin to be treated; and
- 45           4) applying an iontotherapeutically effective, periodic DC  
current of up to about 10mA based on a reservoir elec-  
50           trode/skin-contacting area of about 5 cm<sup>2</sup> using a) a  
periodic waveform in the square, triangular, sinu-  
soidal, trapezoidal, or other acceptable geometric  
55           form, or combinations thereof, b) a physiologically  
acceptable repetition frequency of at least about 10

5 Hz, and c) an on/off ratio of from 1/50 to 10/1; said  
process providing a systemically effective absorption  
10 of said peptide pharmaceutical from said solution at a  
rate of at least 500 percent from that provided by  
passive diffusion transdermal absorption from said  
15 solution during an administration time of at least 2  
hours.

20 The above defined process desirably is carried out  
wherein a sensor is held in intimate contact with the body  
25 of subject being treated such as in intimate contact with  
the skin of the person being treated and said sensor trans-  
mits one or more signals to the control element of the  
30 device such as a physiological factor of the subject being  
treated which correlates with the pharmaceutical administra-  
35 tion carried out by the device or a skin condition which  
relates to the transdermal administration.

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#### BRIEF DESCRIPTION OF THE DRAWINGS

45 FIG. 1 is a diagram portraying a device of the inven-  
tion in operation to effect iontotherapeutic transdermal  
absorption of an ionized pharmaceutical and its uptake into  
50 the bloodstream of the subject treated.

FIG. 2 is a block diagram of a transdermal periodic  
iontotherapeutic device parent application Serial No.  
55 07/046,984.

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FIG. 3 is a block diagram of a transdermal periodic iontotherapeutic device coming within the invention.

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FIG. 4 is a detailed circuit diagram for the Square-Wave Generator shown in FIGS. 2 and 3.

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FIG. 5 is a detailed circuit diagram for the Trapezoidal-Triangular Wave Generator shown in FIGS. 2 and 3.

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FIG. 6 is a detailed circuit diagram for the Sinusoidal Signal Generator shown in FIGS. 2 and 3.

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FIG. 7 is a detailed circuit diagram for the Output Circuit shown in FIGS. 2 and 3.

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FIG. 8 is a block diagram of a wristwatch-type miniaturized periodic iontotherapeutic device coming within the invention, in which the drug reservoir electrode is positioned away from the main portion of iontotherapeutic device.

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FIG. 9A and 9B are diagrams illustrating a wristwatch-type miniaturized transdermal periodic iontotherapeutic system with the drug reservoir electrode positioned directly in the lower portion of the iontotherapeutic device and with multifunctional programmability.

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FIG. 10 is a block diagram of a portable transdermal periodic iontotherapeutic device.

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FIG. 11 and 11A are detailed circuit diagrams of the device shown in FIG. 10.

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FIG. 12 is a detailed circuit diagram showing an electronic timer element which can be used to control the iontotherapeutic administration.

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FIG. 13 is a schematic diagram of a wrist-type ionto-  
therapeutic device coming within the invention showing a  
10 belt-type battery power supply and a sensor for blood sugar  
monitoring.

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FIG. 14 is a schematic diagram showing an iontothera-  
peutic device of this invention in interface with a computer  
system through a connecting line (e.g., interface cable/  
20 telephone line).

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FIG. 15 is a schematic diagram of an iontotherapeutic  
device of this invention using a belt or band to attach to  
the subject being treated.

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FIG. 16 is a graph comparing the effects of periodic  
wave mode and DC mode on the transdermal absorption of insu-  
lin and on the reduction of blood glucose level (B.G.L.) in  
35 the diabetic hairless rats..

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FIG. 17 is a graph showing the time course for the  
reduction in the blood glucose level (B.G.L.) in the dia-  
betic hairless rates as the result of transdermal delivery  
of insulin from a pharmaceutical reservoir electrode con-  
45 taining 250 IU of insulin at pH 3.6 by transdermal periodic  
iontotherapeutic system with square waveform mode (1mA;  
on/off = 1/1; frequency = 2 KHz) for 40 min.

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FIG. 18 is a graph showing the effect of the frequency  
generated by the transdermal periodic iontotherapeutic sys-  
55 tem on the reduction in the blood glucose level (B.G.L.) in  
the diabetic hairless rates using insulin.

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FIG. 19 is a graph showing the effect of the on/off ratio in the transdermal periodic iontotherapeutic system on the reduction in the blood sugar level (B.G.L.) in the diabetic hairless rats using insulin.

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FIG. 20 is a graph showing the effect of the treatment duration by the transdermal periodic iontotherapeutic system with drug reservoir electrode at pH 3.6, on the reduction in the blood glucose level (B.G.L.) in the diabetic hairless rats using insulin.

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FIG. 21 is a graph showing the effect of the treatment duration by the transdermal periodic iontotherapeutic system, with drug reservoir electrode at pH 7.1, on the reduction in the blood glucose level (B.G.L.) in the diabetic hairless rats using insulin.

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FIG. 22 is a graph showing permeation of vasopressin facilitated by the transdermal periodic iontotherapeutic system compared to passive diffusion of a vasopressin solution at pH 5.0 through hairless rat skin.

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FIG. 23A is a graph showing permeation rate of insulin solution at pH 7.1 through hairless rat skin using no iontotherapy as compared to permeation rate shown in FIG. 21B when using iontotherapy (TIDD).

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FIG. 24 is a series of graphs showing the comparative effects of the change in waveform in lowering blood glucose level (B.G.L.) in diabetic hairless rats using transdermal periodic iontotherapeutic system using insulin solution at pH 3.68.

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FIG. 25A is a graph showing lowering of blood sugar level (B.G.L.) of hairless rats using transdermal periodic iontotherapeutic system on Day 1 using insulin solution at pH 3.68.

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FIG. 25B is a graph showing further lowering of the blood sugar levels of the same rats on Day 3 using transdermal periodic iontotherapeutic system without further administration of insulin, indicating that the insulin delivered transdermally on Day 1 is stored in the skin tissues and can be activated to become available for absorption into systemic circulation on Day 3 by TPIS.

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FIG. 26A is a pair of comparative graphs showing plasma immunoreactive insulin levels in diabetic rabbits after administration of insulin solution (pH 7.1) using transdermal periodic iontotherapeutic system (TPIS) compared with corresponding levels in diabetic rabbits using subcutaneous administration (SC). "SZ injection" indicates injections to render rabbits diabetic.

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FIG. 26B is a pair of comparative graphs corresponding to those of FIG. 24A showing the respective reduction of blood glucose levels (B.G.L.). The data show that blood glucose levels can be controlled at a highly constant level so as not to fall substantially, if at all, below normal levels by TPIS.

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FIG. 27A is a pair of comparative graphs showing the increase in plasma insulin concentration after administration of insulin solution (pH 7.10) using transdermal periodic iontotherapeutic system (TPIS) compared to using transdermal iontotherapeutic system (TIDD) in which 4X current intensity and 2X administration times are used. TPIS administration shows more rapid attainment of increased plasma insulin concentrations.

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FIG. 27B is a pair of comparative graphs corresponding to those of FIG. 25A showing the attained lowering of blood glucose levels (B.G.L.). The data show a near instantaneous reduction of blood glucose level from the hyperglycemic level in the diabetic controls using transdermal periodic iontotherapeutic system (TPIS) whereas the reduction using transdermal iontotherapeutic system (TIDD) is lower than the normoglycemic level.

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FIG. 28 is a pair of comparative graphs showing a desired reduction in urine output as indicated by urine osmolarity measurement in anesthetized rabbits using transdermal periodic iontotherapeutic system to administer vasopressin solution (pH 5.0). The corresponding graph shows that TPIS is more effective in reducing urine output than TIDD.

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FIG. 29 is a graph showing vasopressin permeation rate enhancement when the ionic strength of the vasopressin solution used in TPIS is decreased.

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FIG. 30 is a graph showing enhancement of skin permeation of vasopressin using TPIS with a short skin permeation lag time. The graph also shows reversibility of skin permeation within 2 hours after ceasing TPIS treatment and again enhancement of skin permeation after reinstituting TPIS.

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DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

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FIG. 1 is a diagram portraying a device of the invention in operation to deliver iontophoretically an ionized pharmaceutical and its uptake into the bloodstream of the subject being treated. The figure shows the iontophoretic device in electrical contact with the skin.

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It also shows the pharmaceutical reservoir electrode in contact with the skin as well as the other electrode, which is referred to as the receptor electrode. The electrodes are in contact with the uppermost skin barrier, called stratum corneum. The pharmaceutical is transmitted through the stratum corneum and flows into the dermo-epidermal layer. The stratum corneum is the principal absorption rate limiting barrier. The first portion of the dermis layer is referred to as the papillary layer, which contains a capillary network of the vascular system. The capillary network takes up the transdermally absorbed pharmaceutical and the uptaken pharmaceutical is shown to flow from the capillary network into the main portion of the vascular system.

FIG. 2 is a block diagram of a transdermal periodic iontotherapeutic device coming within the invention in which the power supply is derived either from the conversion of the alternate current (AC) from a 120 V-mains (or other available AC mains) into direct current or from a suitable battery. The power is turned on manually by a switch or automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction generators, a drug reservoir electrode and a receptor electrode. The multifunction generator is assembled with a power supply, to delivery direct current with periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeutically-effective waveform can be selected manually or preprogrammed through a switch ( $K_1$ ), and the frequency of the output waveform can be adjusted in the range of 10 Hz - 50 KHz. The output circuit then provides a physiologically acceptable current, for example, ranging up to 10 mA, to the pharmaceutical reservoir electrode which contains the ionized pharmaceutical to be delivered transdermally, and a receptor electrode in series. When desired, the device can be operated to deliver either DC current alone (periodically or continuously), or in combination with a periodic waveform.

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FIG. 3 is a block diagram of an iontotherapeutic device of this invention. It consists of the following elements: a microprocessor, a multiple waveform generator, a waveform selector, an output circuit, a sensor signal processor, a display unit, a power supply with indicator, a reservoir electrode, and a receptor electrode.

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The microprocessor is the center of the device. It has the following functions:

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- a. receiving and processing the physiological signal(s) from the sensor element;
- b. communicating with a computer system via an interface cable;
- c. receiving and exercising commands from the computer system;
- d. storing data and transmitting data to the computer system;
- e. controlling operation parameters of the multiple waveform generator, such as frequency and duty cycle of generated waveforms;
- f. selecting the input waveform of the output circuit;
- g. controlling the operation parameters of the output circuit, such as output current amplitude and treatment cycle;
- h. monitoring the load impedance of the device and alerting the user of improper operation conditions.

5           The microprocessor is made using a commercial single  
chip microcontroller with necessary expanded memory capa-  
10           city, additional input/output ports and signal converters.  
A preferred microcontroller is 80C552 single chip microcon-  
15           troller made by Signetics, a subsidiary of Philips Compo-  
nents. This microcontroller is very powerful and meets the  
requirements of the current application. It has the follow-  
20           ing important features: 16 MHz speed, 8K ROM and 256K RAM  
memory, 4 watchdog timer-counters, 6 I/O ports and 8 channel  
25           12 bit A/D, UART and I<sup>2</sup>C interfaces, and 6 external inter-  
rupts.

30           The multiple waveform generator provides pulse-mode  
signals of desired waveforms. It can be realized by using  
the circuitry shown in FIG. 6. It can also be made by using  
35           a commercial integrated circuit ICL8038 made by Motorola  
Corporation.

40           The waveform selector can be made using a commercial  
electronic analog switch, such as AD7510 made by Analog  
Devices.

45           The output circuit can be made by using the circuit  
design shown in FIG. 7 or using a three-pin constant current  
regulator LM334 made by National Semiconductor Corporation.

50           The function of the sensor signal processor is to fur-  
ther condition the physiological signals, such as blood  
55           glucose level signals. It provides necessary function, such  
as amplification and filtering of the signals. The condi-  
tioned signals will be sent to the analog/digital converter

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of the microprocessor. They will be used for close-loop control of iontotherapeutic treatment.

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The power supply unit consists of battery elements connected in series. The batteries can be either regular ones or rechargeable ones. A low-batter indicator will be used to signal the low battery condition.

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FIG. 4 is a detailed circuit diagram for the square wave generator shown in FIG. 2. It employs a microchip 555 timer. The frequency (F) of the square wave is:

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$$F = \frac{1}{t_1 + t_2} \quad \begin{aligned} t_1 &= 0.693 (P_1 + P_2) C \\ t_2 &= 0.693 P_1 C \end{aligned}$$

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where P's are potentiometers, C is a capacitor, and D's are diodes. During the operation, the capacitor C is charged through the potentiometer P<sub>1</sub> and P<sub>2</sub> and the diode D for t<sub>1</sub> seconds and discharged through potentiometer P<sub>1</sub> and diode D<sub>2</sub> for t<sub>2</sub> seconds. Other circuits can be used in place thereof.

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FIG. 5 is a detailed circuit diagram for the triangular-trapezoidal waveform generator shown in FIG. 2. It consists of an integrator (A) and a regenerative comparator (B) connected in a positive feedback loop. Precise triangular waves are formed by integration of the square wave which is fed back from the output of the comparator to the input of the integrator. The frequency (F) of the triangular wave is:

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$$F = \frac{1}{t_1 + t_2} \frac{t^1 = V_{o+} - V_{o-}) R^1}{R_2} \frac{V_{o+}}{C (P_2 a + P_3 b)}$$

$$\frac{t^1 = V_{o+} - V_{o-}) R^1}{R_2} \frac{-V_{o-}}{C (P_2 a + P_3 b)}$$

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where  $V_{o+}$  and  $V_{o-}$  are the higher and lower trip points of the comparator, respectively. Resistors  $R_1$  and  $R_2$  control the comparator trip points. Capacitor  $C$  is the integration capacitor. Potentiometer  $P_1$  provides adjustment of the triangular wave offset. Potentiometers  $P_2$  and  $P_3$  adjust frequency and symmetry, respectively.

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The third op-amp circuit (C) acts as a damper. It produces a trapezoidal wave with the same frequency as the triangular wave. Potentiometer  $P_4$  sets the clamping level. Other circuits can be used in place thereof.

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FIG. 6 is a detailed circuit diagram for the sinusoidal signal generator shown in FIG. 2. The circuit of the generator uses two amplifiers: one (A) acts as a non-inverting integrator, and other (B) acts as an inverting integrator. They are connected in cascade to form a feedback loop. The frequency (F) of the sinusoidal signal is determined by:

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$$F = \frac{1}{2 CP}$$

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C's and P's are integration capacitors and the variable resistors, respectively. Resistor  $R_1$  is a feedback resistor. Capacitor  $C_1$  is used to prevent high-frequency oscillations. Other circuits can be used in place thereof.

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FIG. 7 is a detailed circuit diagram for the Output Circuit shown in FIG. 2. The desired waveform is selected manually or automatically from the 3 generators through a switch ( $K_1$ ) and sent to the inverting amplifier, from which the signal then goes to the output stage of two transistors. The output current (dose current) is adjusted by a potentiometer (P), as monitored by a current meter (A), and is delivered to the drug reservoir electrode (B). Other circuits can be used in place thereof.

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FIG. 8 is a diagram illustrating the wristwatch-type miniaturized transdermal periodic iontotherapeutic system with multifunction programmability. It is designed to have one or more nuclear batteries and two pieces of microchips: one for the purpose of generating different waveforms, as outlined in FIGS. 4-6, and the other is for the purpose of controlling and to display the output current. The nuclear batteries provide the energy needed for long-term operation. For instance, the programmability may include selection of DC alone or in combination with a periodic waveform, a dose current for a particularly designated time period. In certain applications, it may be advantageous in operating the devices of this invention to have the periodic current wave-



5 form remaining at some constant DC level during the off  
cycle. In this design of iontotherapeutic device, the drug  
10 reservoir electrode is positioned outside the device.

FIG. 9 shows an embodiment of another design of ionto-  
15 therapeutic device. It shows two views of the device. The  
first view is a cross-sectional view showing the integrated  
circuitry, L.C. display, battery, drug reservoir electrode  
20 positioned directly in the lower central portion of the base  
and the receptor electrode encircling the drug reservoir  
electrode. The next view shows the bottom view of the  
25 device. In the center portion of the bottom view is shown  
the circular drug reservoir portion of the drug reservoir  
electrode. The drug or pharmaceutical dissolved in an  
30 aqueous solution is homogeneously dispersed in a polymer  
matrix unit dose as described herein. The pharmaceutical  
35 solution can also be contained in a reservoir-type unit dose  
having a microporous surface adapted to permit the drug to  
40 be transmitted. Next, there is shown the receptor elec-  
trode, as a circular ring positioned in spaced relationship  
45 from the drug reservoir electrode. At the top of the cross-  
sectional view is shown a liquid crystal display. It can  
display a number of functions, including whether or not the  
50 device is in operation, the type of periodic current and  
waveform being used and other pertinent information of the  
transdermal periodic iontotherapeutic drug delivery. The  
55 battery employed as the power source for this invention can

5 be a lithium or other nuclear battery having a voltage, for example, of from 6 to 12 volts.

10 FIG. 10 is a block diagram of a portable transdermal periodic iontotherapeutic device in which the power supply is derived from a battery source such as one or more 9V  
15 batteries. The power is turned on manually by a switch. The device can be equipped so that it can be turned on automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction  
20 generators, a drug reservoir electrode and a receptor electrode. The multifunction generator can provide periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeutically effective waveform can be selected manually and  
25 the frequency of the output waveform can be adjusted to a physiologically acceptable frequency of at least 10 Hz and up to about 50 KHz. The output circuit then provides a  
30 physiologically acceptable current, ranging up to 10 mA, to the pharmaceutical reservoir electrode, which contains the solution of the ionized pharmaceutical to be delivered transdermally, and a receptor electrode in series. When  
35 desired, the device can be operated to deliver either DC current alone (periodically or continuously), or in combination with a periodic waveform.

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55 FIGS. 11 and 11A show a detailed circuit diagram for the portable transdermal periodic iontotherapeutic device shown in the block diagram of FIG. 10. Referring to FIG.

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11, the following is a description of the circuits and their  
functioning:

10  
The DC-to-DC converter and battery voltage monitor

15  $1C_1$ ,  $R_1$ - $R_4$ ,  $C_1$ - $C_3$ ,  $L_1$  and diode IN914 consist of a DC-to-DC converter which is incorporated in step-up application. The output voltage is elevated from 9V battery to 27V  
20 with the proper adjustment of  $R_4$ . The output voltage of the battery is monitored by a battery voltage monitor which includes a zener diode  $D_1$ ,  $R_5$ - $R_7$ ,  $C_4$  and C106Y1. When out-  
25 put of 9-V battery drops below minimum acceptable volume of 8.3V, LED lights to indicate the need for recharging.

30  
Pulse generator and constant current output stage

35  $IC_2$ ,  $D_2$ - $D_5$ ,  $T_1$ ,  $C_5$ ,  $C_6$  and  $R_8$  are components of a triangle-wave generator. In this circuit, the charge and discharge currents for  $C_6$  come through the diode bridge formed by  $D_2$ - $D_5$ . Bridge  $D_2$ - $D_5$  consists of four general  
40 purpose switching diodes with low-leakage characteristics, that serve to steer current in the proper direction through the current source made up of  $T_1$  and  $R_8$ .  
45

50 The pin 3 of  $IC_2$  serves as a source of current for the timing network, and its state of high or low determines the direction of current flow into or out of  $C_6$  for charge or discharge. Since both charge and discharge currents flow  
55 through the same current regulator circuit, the currents are

5 equal, and thus times of charge and discharge are equal. As  
a result, triangular waves are formed across  $C_6$ .

10 The circuit covers the frequency range of about 20 Hz  
to 30 KHz. The adjustment of the frequency is done with  $R_8$ .  
The frequency of the triangle waves can be expressed as

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$$f = \frac{1}{5R_8C_6}$$

20 The output of the triangle-wave generator is sent to  
the pin 3 of  $IC_3$  which serves as a comparator. The voltage  
comparison is made between pin 1 and pin 3 of  $IC_3$ . The  
25 square waves are formed at pin 7 of  $IC_3$  with a duty cycle  
which is determined by the voltage of the voltage divider  
composed of  $R_{10}$ - $R_{12}$ . The higher the voltage applied to pin  
30 2 is, the shorter the "on" time of the square waves, and  
vice versa. The duty cycle of the square waves covers the  
35 range of 1/10 to 10/1. The square waves are amplified by  
 $T_2$ - $T_4$  and sent to pin 11 of  $IC_4$ .

40 In constant current output stage,  $IC_{923}$  is employed to  
serve as a current regulator.  $IC_{923}$  is originally designed  
to be a voltage regulator with an output current limit  
45 resistor  $R$  across pin 10 and pin 3. The maximum output  
current is set as  $0.6/R$ . This feature is adapted to form a  
current regulator. As soon as the condition  $(V_{out}/R_L) > I_S$  is  
50 satisfied (where  $V_{out}$  is the output voltage,  $R_L$ , load resis-  
tance, and  $I_S$ , output current preset), the output current  
55 will be kept at the preset level.

5

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$R_{21}$  is the minimum current limit resistor.  $R_{22}$  is used to preset the desired output current.  $C_7$  and  $R_{20}$  are used to eliminate high frequency noise.

#### Output current monitor

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Intersil 7106 interfaced with a liquid crystal display is the heart of the current monitor.  $R_{23}$  is a shunt resistor.  $C_8$  and  $R_{24}$  consist of an RC oscillator which runs at about 48 KHz and is divided by four prior to being used as the system clock.  $C_{10}$  and  $R_{27}$  serve as an input filter.  $C_{11}$ ,  $C_{12}$  and  $R_{28}$  determine the display sensitivity.  $C_9$  is for auto-zero function.

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The power is turned on manually by a switch or automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction generators, a drug reservoir electrode and a receptor electrode. The multifunction generator is assembled with a power supply, to deliver direct current with periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeutically effective waveform can be selected manually or programmed through a switch ( $K_1$ ), and the frequency of the output waveform can be adjusted in the range of 10 Hz - 50 KHz. The output circuit then provides a physiologically acceptable current, ranging up to 10 mA, to the pharmaceutical reservoir electrode, which contains the pharmaceutical formulation to be delivered transdermally, and a receptor

5 electrode in series. When desired, the device can be  
operated to deliver either DC current alone (periodically or  
10 continuously), or in combination with a periodic waveform.

FIG. 12 is a detailed circuit diagram for the timer of  
15 the multi-channel transdermal periodic iontotherapeutic  
device shown in the block diagram of FIG. 12. Referring to  
FIG. 12, the following is a description of the circuit, and  
20 their functioning:

#### Timer

25 The timer consists of ten IC chips, two relays and  
other components, IC<sub>8</sub> provides a system clock. IC<sub>1</sub>, IC<sub>3</sub> and  
30 IC<sub>5</sub> are quad 2-input multiplexers which consist of four 2-  
input multiplexers with common select and enable inputs.  
When the select input is at logical "0", the four output  
35 pins assume the values of inputs of pin 1, 5, 14, 11, other-  
wise, inputs of pin 3, 6, 13, 10. The inputs of the first  
group represent the "off" time of the timer which has a  
40 maximum value of 999 minutes. The inputs of the second group  
represent the "on" time of the timer which has a maximum  
45 value of 99 minutes. The values of both "on" and "off" time  
needed are set through BCD thumbwheels.

50 IC<sub>2</sub>, IC<sub>4</sub> and IC<sub>6</sub> are "decade-down" counters which  
receive preset values from multiplexers. The pin 15's of  
these counters will become logical "0" when the minimum  
55 count is reached. When all three counters reach the mini-  
mum, IC<sub>9</sub>, a "AND" gate, will turn to be logical "1". This

5 pulse is inverted by  $IC_{10}$  and goes to reset the system  
clock, reloads counters and converts  $IC_7$ , which consists of  
10 two Flip-Flop's. At the instant when "on" time is finished,  
the pin 3 and pin 5 turn to be logical "0", which opens two  
15 relays and turns on the red LED. AT the same time, the pin  
2 and pin 6 turns to be logical "1", which will load the  
values representing the "on" time to pin 4, 7, 9, 12 of  
20 three multiplexers and turns off the green LED. At the  
instant when "off" time is finished, the pin 3 and pin 5  
25 turn to be logical "1", which will load the values repre-  
senting the "off" time to pin 4, 7, 9, 12 of three multi-  
plexers and turns on the green LED. The whole cycle of both  
30 "on" and "off" is repeated for any desired length of time.  
The switch  $K_2$  is used to interrupt the operation and trigger  
35 the timer.

#### Pulse generator and constant current output stages

40  $IC_{13}$ , diode bridge consisting of four  $IN_{914}$ ,  $T_1$ ,  $R_{28}$   
and  $C_5$ - $C_7$  are components of a triangle wave generator. In  
this circuit, the charge and discharge currents for one of  
45  $C_6$ - $C_{17}$  come through the diode bridge formed by four  $IN_{914}$ ,  
which serve to steer current in the proper direction through  
50 the current source made up of  $T_1$  and  $R_{28}$ .

The pin 3 of  $IC_2$  serves as a source of current for the  
timing network, and its state of high or low determines the  
55 direction of current flow into or out of the capacitor for  
charge or discharge. Since both charge and discharge cur-

5 rents flow through the same current regulator circuit, the  
currents are equal and thus times of charge and discharge  
10 are equal. As a result, triangular waves are formed across  
the working capacitor C.

15 The circuit covers the frequency range of about 10 Hz  
to 30 KHz. The adjustment of the frequency is done by the  
selection of the proper capacitor through a multi-stop  
20 switch. The frequency of the triangle waves can be  
expressed as

$$25 \quad f = \frac{1}{5R_{28}C}$$

The output of the triangle wave generator is sent to  
30 the pin 3 of IC<sub>14</sub> which serves as a comparator. The voltage  
comparison is made between pin 2 and pin 3 of IC<sub>14</sub>. The  
square waves are formed at pin 7 of IC<sub>14</sub> with a duty cycle  
35 which is determined by a voltage-divider composed of R<sub>322</sub>-  
R<sub>34</sub>. The higher the voltage applied to pin 2 is, the short-  
40 er the "on" time of the square waves, and vice versa. The  
duty cycle of the square waves covers the range of 1/10 to  
10/1. The square waves are amplified by T<sub>2</sub> and T<sub>3</sub> and then  
45 sent to three voltage followers T<sub>4</sub>-T<sub>6</sub>.

At the "on" time of the timer, two relays are closed  
50 and emitters of T<sub>4</sub>-T<sub>6</sub> are connected to pin 11's of IC<sub>15</sub>-  
IC<sub>17</sub>. IC<sub>15</sub>-IC<sub>17</sub> provide three-channel current outputs.  
Three IC<sub>923</sub> are employed to serve as current regulators.  
55 IC<sub>923</sub> is originally designed to be a voltage regulator with  
an output current limit resistor R across pin 10 and pin 3.



5           The maximum current is set as  $0.6/R$ . This feature is  
10       adapted to form a current regulator. As soon as the condition  $(V_{out}/R_L) > I_S$  is satisfied (where  $V_{out}$  is the output  
15       voltage,  $R_L$  load resistance and  $I_S$  output current preset), the output current  
      will be kept at the present level.  $R_{40}$ ,  $R_{45}$  and  $R_{50}$  are  
20       maximum current limit resistance respectively.  $R_{41}$ ,  $R_{46}$  and  
       $R_{51}$  are used to preset the desired current.  $C_{19}$ - $C_{21}$  are  
      used to eliminate high frequency noise.

25           The output currents are monitored by a current meter A.  
      The switch  $K_1$  is used to select DC or pulse output. Other  
30       circuits can be used in place thereof.

35           FIG. 13 is a schematic diagram of a device of this  
      invention. It shows a wristwatch-type device which houses  
40       the iontotherapeutic device in the center in connection with  
      a belt-type battery package. The display unit, emergency  
      on/off switch, the input/output port, the interface cable to  
45       a computer system, and the sensor input port are also shown.  
      This device can be comfortably worn by a patient during the  
      treatment. The weight of such device of this invention will  
      ordinarily be 5 oz. or less, preferably 3 oz. or less.

50           FIG. 14 is a schematic diagram of a wrist-type ionto-  
      therapeutic device of this invention showing a connection  
      with a computer patient data and control system such as at a  
55       clinical site or at a physician's office. The communication  
      between the iontotherapeutic device and a computer system

5 serves two purposes. It allows the commands and data  
according to the physician's prescription to transfer to the  
10 iontotherapeutic device via an interface cable. It also  
allows the physician to read and assess the important data  
of treatment using the device. By using telephone lines,  
15 the communication can be to a remote site.

Various computers are satisfactory for use in the com-  
puter system, including personal computers and larger compu-  
20 ters. Various suitable programs can be used in the communi-  
cation.

25 FIG. 15 is the schematic diagram of an iontotherapeutic  
device of this invention using a belt or band to attach to  
the subject being treated. Inside the belt there are bat-  
tery elements connected in series. These batteries can be  
either regular ones or rechargeable ones. The battery belt  
35 can also be made into a shape of jewelry. The battery belt  
can be designed to house different numbers of battery ele-  
ments to power different treatment periods. The belt can be  
40 made of suitable material such as plastic or leather mate-  
rials or metals or combinations of materials. Its length  
45 can be adjusted as needed.

FIG. 16 is a graph showing the time course for the  
50 reduction of the elevated blood glucose level (% change in  
B.G.L.) in the diabetic hairless rats as the result of  
transdermal delivery of insulin from the drug reservoir  
55 electrode (containing 250 IU of insulin at pH 7.1) by Trans-  
dermal Periodic Iontotherapeutic System for 80 minutes and

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the effect of current delivery mode. Keys: (O) direct  
current mode (2 mA), ( ) Square wave periodic mode (2 mA;  
on/off = 4/1; Frequency = 2000 Hz).

FIG. 17 is a graph showing the time course for the  
reduction of the elevated blood glucose level (% change in  
B.G.L.) in the diabetic hairless rats as the result of  
transdermal delivery of insulin from the pharmaceutical  
reservoir electrode (containing 250 IU of insulin at pH 3.6)  
by Transdermal Periodic Iontotherapeutic System with square  
wave periodic mode (1 mA; on/off = 1/1; Frequency = 2000 Hz)  
for 40 minutes.

FIG. 18 is a graph showing the effect of the frequency  
generated by the Transdermal Periodic Iontotherapeutic Sys-  
tem on the reduction of the elevated blood glucose level (%  
change in B.G.L.) in the diabetic hairless rats. The fre-  
quency of 2000 Hz produces a greater magnitude and a longer  
duration of reduction than the 1000 Hz.

FIG. 19 is a graph showing the effect of the on/off  
ratio in the Transdermal Periodic Iontotherapeutic System on  
the reduction of the elevated blood glucose level (% change  
in B.G.L.) in the diabetic hairless rats. By regulating the  
ratio, the magnitude and the duration of reduction in B.G.L.  
in the diabetes can be controlled as desired.

FIG. 20 is a graph showing the effect of the treatment  
duration by the Transdermal Periodic Iontotherapeutic System  
on the reduction of the elevated blood glucose level (%  
change in B.G.L.) in the diabetic hairless rats.

5 change in B.G.L.) in the diabetic hairless rats. At pH 3.6,  
which is lower than the isoelectric point of insulin (pH  
10 5.3), with the dose current of 1 mA, on/off ratio of 8/1 and  
at a frequency of 2000 Hz, the treatment duration of 20-40  
15 minutes appears to be equally effective.

FIG. 21 is a graph showing the effect of the treatment  
duration by the Transdermal Periodic Iontotherapeutic System  
20 on the reduction of the elevated blood glucose level (%  
change in B.G.L.) in the diabetic hairless rats. AT pH 7.1,  
which is higher than the isoelectric point of insulin (pH  
25 5.3), with the dose current of 1 mA, on/off ratio of 1/1 and  
at frequency of 1000 Hz, the treatment duration produces a  
30 difference in the rate and the duration, but with equal  
effectiveness.

35 For a more detailed description of the background for  
the remaining FIGS., see the indicated Examples: FIG. 22  
(Example 11); FIGS. 23A and 23B (Example 12); FIG. 24  
40 (Example 14); FIG. 25 (Example 15); FIGS. 26A and 26B  
(Example 16); FIG. 27 (Example 17); FIG. 28 (Example 18);  
45 FIG. 29 (Example 19); FIG. 30 (Example 20).

In carrying out the iontotherapeutic process for admin-  
istering transdermally, systemically measured amounts of an  
50 ionized pharmaceutical compound, it is first necessary to  
provide the pharmaceutical-containing unit dose in which the  
pharmaceutical is in aqueous solution. The pH of the  
55 aqueous solution is adjusted to an effective Ph either below  
or above the pKa or the isoelectric point of the pharmaceu-

5                   tical. It is desirable to adjust the pH to an effective  
10                   level of about 1 pH unit above or below the pKa or isoelec-  
                  tric point of the pharmaceutical, preferably to an effective  
15                   pH level of at least 1.5 or at least 2 pH units below or  
                  above the pKa or isoelectric point of the pharmaceutical.  
20                   With particular pharmaceuticals, it is preferable to so  
                  adjust the pH either below or above the pKa or isoelectric  
                  point. For example, with regard to insulins, it is prefer-  
25                   able to adjust the pH below the pKa or isoelectric point,  
                  such as to about 1.0 pH units or lower below, which for  
                  commercial insulins is about pH 5.3.

30                   The formed unit dose is placed in the receptacle por-  
                  tion provided in the pharmaceutical reservoir electrode, so  
                  that the ionized pharmaceutical can be transdermally  
35                   absorbed. If the unit dose form is a preformed self-con-  
                  tained unit dose, it can be held in the receptacle portion  
40                   of the reservoir electrode by customary means such as clamp-  
                  ing, snapping into position, adhesive, or the like.

45                   One convenient form of the unit dose for the ionized  
                  pharmaceutical solution is to disperse uniformly the aqueous  
                  solution of the ionized pharmaceutical in a polymeric  
50                   matrix. The polymeric unit dose must be characterized by  
                  being able to release the ionized pharmaceutical, when the  
                  iontotherapeutic device is in operation, so that the ionized  
55                   pharmaceutical can be absorbed transdermally. The unit dose

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is in electrical contact with the skin of the subject being treated when the iontotherapeutic device is in operation.

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For a description on making suitable unit dose in the form of a polymeric matrix dosage unit, reference is made to parent U.S. Application Serial No. 07/046,984, filed May 5, 1987, now U.S. Patent Application No. 5,042,975, which is incorporated herein by reference.

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Additionally, descriptions are found in parent U.S. Application Ser. No. 07/587,406, filed September 25, 1990, which is incorporated herein by reference.

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The pharmaceuticals suitable for delivery by this polymer disc can be the anti-diabetic drugs, such as insulins or sulfonyl ureas; the anti-diuretic peptide drugs, such as vasopressin; the calcium-channel blocker-type anti-hypertensive drugs, such as verapamil; the beta-blocker type anti-hypertensive drugs, such as propranolol; narcotic analgesic drugs, such as hydrocodone; non-steroidal anti-arthritic drugs, such as indomethacin; anti-bacterial antibiotics, such as tetracyclines, penicillins and cephalosporins; anti-neoplastic drugs, such as methotrexate; and the peptide hormones, such as luteinizing hormone-releasing hormone (LHRH), oxytocin, and the like.

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Pharmaceuticals suitable for use in the process of this invention can be selected from the following or other ionizable pharmaceuticals which are capable of being transdermally absorbed in the iontotherapeutic process, the following systemically-effective pharmaceuticals expected to be

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capable of delivery by an iontotherapeutic device as  
developed in this invention: Propranolol HCl, Ibuprofen,  
Indomethacin HCl, Lorazepam, Thioridazine HCl, Tolazamide,  
Doxycycline, Flurazepam, Minocycline, Disopyramide, Meto-  
cloprimide HCl, Cephalothin sodium, Thiothixene, Vincris-  
tine, Oxazepam, Valproic acid, Temazepam, Hydralazine HCl,  
Ampicillin sodium, Amantadine HCl, Acetohexamide, Haloperi-  
dol, Doxepin, Cyclobenzaprine HCl, Sucralfate, Cephalaxin,  
Cefazolin sodium, Ampicillin, Cefadroxil, Hydralazine HCl,  
Reserpine and Hydrochlorthiazide, Clindamycin HCl, Carbeni-  
cillin disodium, Piroxicam, Fenoprofen calcium, Diltiazem  
HCl, Chlorpropamide, Sulindac, Nefedipine, Cimetidine,  
Naproxen, Piroxicam, Ranitidine HCl, Nadolol, Alprozolam,  
Captopril, Triazolam, Chlordiazepoxide, Amitryptilline,  
Dobutamide, Sulfamethoxazole, Trimethoprin, and the like.

The ionizable peptide pharmaceuticals used in the  
processes and the unit doses of this invention and adminis-  
tered by the devices of this invention are those which are  
pharmaceutically effective and transdermally absorbable.  
Desirably the peptides have at least five amino acid units  
and more desirably at least nine amino acid units.

In operating the process, using for example a wrist-  
watch-type iontotherapeutic device such as provided by this  
invention, the appropriate unit dose containing the pharma-  
ceutical required for the desired therapy is assembled in  
the receptacle portion of the pharmaceutical reservoir elec-

5 trode. For example, if insulin is to be administered and  
the pH of the insulin solution in the dose unit is pH 3.6,  
10 insulin is a cationic and therefore the dosage unit is  
assembled as a part of pharmaceutical reservoir electrode,  
15 which is the anode. The desired waveform is selected and  
preprogrammed, such as a square waveform. The pharmaceuti-  
cal reservoir electrode used preferably is adapted to  
20 receive a disposable unit dose, e.g., a polymeric matrix  
unit dose, and to make electric contact with the skin of the  
subject being treated. Such means is assembled in place.  
25 The other variables are selected and preprogrammed, such as  
the frequency, the dose current and on/off ratio. The  
30 device is attached to the subject being treated as by a band  
attached to the device and adapted to be attached to and  
detached from the subject. The switch of the device is  
35 turned to "on" position and the device commences operation  
of the iontotherapeutic process, which causes the ionized  
40 pharmaceutical of reservoir electrode to be administered  
transdermally and iontotherapeutically to provide a systemic  
dosing. The particular waveform, mA, pharmaceutical reser-  
45 voir electrode (i.e., cathode or anode), frequency, length  
of treatment and other factors will be selected and prepro-  
50 grammed depending upon the pharmaceutical being admin-  
istered, the subject being treated and others.

55 Some pharmaceuticals, especially certain relatively low  
molecular weight pharmaceuticals, can be iontotherapeuti-  
cally administered using either periodic DC mode or periodic



5 wave mode. For example, the periodic DC mode can be "on"  
10 for about 0.5 to about 10 minutes, preferably about 1 to  
about 5 minutes per hour. During the intervening period  
15 during the hour, the device is in "off" position. The "on"  
period can be more frequent or less frequent, if desired, to  
provide effective treatment, such as one "on" period every  
20 30 minutes or every ninth minute. In Example 5, it is shown  
that hydrocodone can be administered following this general  
procedure. The dose currents, the on/off ratios, the dosage  
25 units and the devices described above can be used or adapted  
to be used in the practice of the periodic DC mode process.

30 A few hours duration of treatment each day following  
either procedure is ordinarily adequate, for example, 2 to  
35 10 hours, depending upon factors such as the pharmaceutical,  
the subject being treated, the iontotherapeutic factors  
selected and the like.

5           The following Examples are illustrative of the inven-  
tion but are not intended to be limiting.

10       Example 1

15           An aqueous solution of insulin at concentration of 250  
IU/ml is prepared by dissolving 96.9 mg (25.8 IU/mg) of pure  
insulin in 10 ml of double-distilled, sterile water and  
20       adjusted to pH 7.1 with 0.5N NaOH. Two ml of the insulin  
solution so prepared is filled into a refillable dosage unit  
having a microporous membrane as the drug-releasing surface.  
25       This insulin-containing reservoir-type dosage unit is then  
assembled as a part of the pharmaceutical reservoir elec-  
trode and applied on the abdominal skin of 3 diabetic hair-  
30       less rats with the transdermal periodic iontotherapeutic  
system operating at 2 mA with direct current mode or square-  
35       wave periodic mode (on/off = 4/1; Frequency = 2000 Hz). The  
results on the reduction in blood glucose level are shown  
and compared in FIG. 16.

40       Example 2

45           An amount of 200 mg (25.8 IU/mg) of pure insulin is  
dissolved in 10 ml of double-distilled, sterile water and  
the pH is adjusted to 3.6 with 0.5N HCl. An amount of 200  
50       mg of hydroxypropylmethylcellulose is well dispersed in  
another 10 ml of double-distilled sterile water using a  
55       magnetic stirrer with a stirring bar (5 cm in length) at a  
rotation speed of 600 rpm. The temperature is controlled at

5 about 80°C. After the hydroxypropylmethylcellulose is dis-  
persed homogeneously, the stirring is continued while the  
10 mixture is cooled to about 40°C.

The insulin solution prepared above is then added to  
15 the dispersion of hydroxypropylmethylcellulose with inter-  
mittent stirring to avoid any denature of insulin molecules,  
using the same stirring mechanism as described above, at the  
20 same stirring rate of 600 rpm for a period of two minutes.  
The insulin/hydroxypropylmethylcellulose solution is then  
25 placed in a refrigerator for congealing to occur. The insu-  
lin-containing polymer matrix is cut into disc-shaped parts  
with the appropriate dimensions, such as 2.5 cm in diameter  
30 and 0.2 cm in thickness. The insulin-containing discs are  
stored at 5°C. The concentration of insulin in the discs is  
35 about 250 IU/gm.

The insulin-containing polymeric matrix dosage forms  
are removed as needed and assembled into the pharmaceutical  
40 reservoir electrode. The pharmaceutical reservoir electrode  
having the insulin-containing polymer unit dose form is the  
45 anode since the insulin molecules in the polymeric matrix  
dose units are cations at pH 3.6, which is lower than the  
isoelectric point of insulin (pH<sub>iso</sub> = 5.3).

50 Application of this insulin-containing polymeric matrix  
unit dose is made onto the abdominal skin of 3 diabetic  
hairless rats. The transdermal periodic iontotherapeutic  
55 system is then operated at 1 mA using an on/off ratio of  
1/1, a frequency of 2000 Hz and a square wave mode, for 40

5 minutes. The result on the reduction in blood glucose level is shown in FIG. 17.

#### 10 Example 3

15 An aqueous solution of insulin at a concentration of 250 IU/ml is prepared by dissolving 193.8 mg (25.8 IU/mg) of pure porcine insulin in 20 ml of citrate buffer at pH 3.6. 20 Two ml of the insulin solution so prepared is filled into a refillable dosage unit having a microporous membrane as the drug-releasing surface. This insulin-containing reservoir-type dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device 25 and applied successively on the abdominal skin of 9 diabetic hairless rats with the transdermal periodic iontotherapeutic system operating at 1 mA with square waveform mode to study 30 the effect of frequency, on/off ratio and treatment duration on the reduction of blood glucose level. The results are shown and compared, respectively in FIGS. 18, 19 and 20. 35 40

#### 45 Example 4

50 The same insulin solution is prepared in the same way as in Example 1, except that a phosphate buffer at pH 7.1 is used to replace the double-distilled water. Two ml of the insulin solution so prepared is filled into a refillable dosage unit having a microporous membrane as the drug-releasing surface. This unit dose is applied to 3 diabetic 55 hairless rats following the same operation procedures as in

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Example 3 to study the effect of treatment duration on the reduction of blood glucose level. The results are shown in FIG. 21.

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#### Example 5

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A saturated solution of hydrocodone ( $pK_a = 8.56$ ), a narcotic analgesic drug, is prepared in citrate buffer at pH 4.0 and in phosphate buffer at pH 7.5. An aliquot of 3.5 ml of this hydrocodone solution is filled into the reservoir compartment, which is in contact with the stratum corneum surface of the hairless rat abdominal skin, of each Valia-Chien skin permeation cell with the receptor compartment containing equal volume of a pH 7.4 buffered isotonic (drug-free) saline solution. The transdermal periodic iontopherapeutic system is then mounted with its electrodes immersing in the skin permeation cell, one electrode in each of the two solution compartments. A current of 1 mA is applied for 2 min. periodically on the hour for 12 hours at either DC mode or periodic square wave mode (frequency, 2000 Hz; on/off ratio, 1/1). The results are shown in Table I.

Table I: Enhancement in Rate and Reduction in Time Lag of the Skin Permeation Rate of Hydrocodone, a Narcotic Analgesic Drug, by the Transdermal Periodic Iontotherapeutic System

<u>Skin Permeation Rate</u> (mcg/cm <sup>2</sup> /hr $\pm$ S.D.)			
Mode	pH 7.5	pH 4.0	T <sub>lag</sub> (hrs)
Control	4.75 $\pm$ 1.70	3.10	5.17
DC mode	7.61 $\pm$ 2.74	37.5	0.72
periodic wave mode	7.01 $\pm$ 1.16	59.4	0.90

#### Example 6

A saturated solution of methotrexate, an anti-neoplastic drug, is prepared in double-distilled water and adjusted to pH 8.0, which is higher than the pKa values of methotrexate (4.8 and 5.5). An aliquot of 3.5 ml of this methotrexate solution (2 mg/ml) is filled into the donor compartment, which is in contact with the stratum corneum surface of the hairless rat abdominal skin, of each Valia-Chien skin permeation cell with the receptor compartment containing equal volume of a pH 7.4 buffered isotonic (drug-free) saline solution. The transdermal periodic iontotherapeutic system is then mounted with its electrodes immersed in the skin permeation cell, one electrode in each of the two solution compartments. A DC current of 1 mA is applied for 10 minutes periodically on the hour for 5 hours with a frequency of 2000 Hz, a square wave form, and an on/off ratio of 4/1. The results are illustrated in Table II:

Table II: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Methotrexate - An Anti-Neoplastic Drug

Time	Cumulative Amount of Drug Absorbed (mcg/cm <sup>2</sup> )	
(hrs)	No TPIS	With TPIS
1.33	0.0086	0.0820
2.33	0.0247	0.1373
3.33	0.0471	0.4223
4.16	0.0745	0.5705
5.16	0.1398	1.0835

Example 7

A saturated solution of propranolol (pKa = 9.45), a beta-blocker type anti-hypertensive drug, is prepared in citrate buffer at pH 3.68. The enhancing effect of the transdermal periodic iontotherapeutic system is studied under the same conditions as that outlined in Example 6. The results are shown in Table III:

Table III: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Propranolol <sup>(1)</sup> - An Anti-Hypertensive Beta-Blocker Drug

Time (hrs)	Cumulative Amount of Drug Absorbed (mcg/cm <sup>2</sup> )	
	No TPIS	With TPIS <sup>(2)</sup>
1.5	0.0691	0.5970
2.5	0.2615	1.1950
3.5	0.5845	3.3650
4.5	0.9955	5.2150
5.5	2.0800	9.0700

- 1) In the Valia-Chien skin permeation cell, a donor solution containing 13.3 mg/ml of propranolol (pKa = 9.45) at pH 3.68 was applied topically to hairless rat skin at 37°C.
- 2) TPIS applied a DC current of 1mA periodically at 10 min/hr, a frequency of 2000 Hz and an on/off ratio of 4/1.

#### Example 8

A saturated solution of verapamil (pKa = 8.9), a calcium-channel blocker-type anti-hypertensive drug, is prepared in citrate buffer at pH 3.68. The enhancing effect of the transdermal periodic iontotherapeutic system is studied under the same conditions as that outlined in Example 6. The results are shown in Table IV.



Table IV: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Verapamil<sup>(1)</sup> - A Calcium-Channel Blocker-Type Antihypertensive Drug

Time (hrs)	Cumulative Amount of Drug Absorbed (mcg/cm <sub>2</sub> )	
	No TPIS	With TPIS <sup>(2)</sup>
1.42	<0.0001	0.297
2.42	<0.0001	0.445
3.42	-	0.695
4.17	-	0.973
5.17	<0.0001	1.945

- 1) In the Valia-Chien skin permeation cell, a donor solution containing 23.95 mg/ml of verapamil (pKa = 8.9) at pH 3.68 is applied topically to hairless rat skin at 37°C.
- 2) TPIS applied a DC current of 1 mA periodically at 10 min/hr, a frequency of 2000 Hz and an on/off ratio of 4/1.

#### Example 9

A saturated solution of tetracycline HCl (pKa = 3.3, 7.8 and 9.7), an antibiotic drug, is prepared in phosphate buffer at pH 9.0. The enhancing effect of the transdermal periodic iontotherapeutic system is investigated under the same conditions as that outlined in Example 6. The results are shown in Table V:

Table V: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Tetracycline HCl<sup>(1)</sup> - A Calcium-Channel Blocker-Type

10	Time	Cumulative Amount of Drug Absorbed (mcg/cm <sub>2</sub> )	
	(hrs)	No TPIS	With TPIS <sup>(2)</sup>
15	1.25	0.0180	0.1765
	2.25	0.0550	0.2555
	3.25	0.0650	0.7815
	4.25	0.1450	1.3235
20	5.25	0.3040	3.5600

- 1) In the Valia-Chien skin permeation cell, a donor solution containing 6.2 mg/ml of tetracycline HCl (pKa = 3.3, 7.8 and 9.7) at pH 9.0 is applied topically to hairless rat skin at 37°C.
- 2) TPIS applied a DC current of 1 mA periodically at 10 min/hr, a frequency of 2000 Hz, a square waveform and an on/off ratio of 4/1.

#### Example 10

A saturated solution of indomethacin (pKa = 4.5), a non-steroidal anti-arthritic drug, is prepared in buffer solution at pH 2.5, which is 2 pH units below the pKa, and at pH 5.5, which is one pH unit above the pKa, and at pH 4.5, the pKa. The enhancing effect of the transdermal periodic iontotherapeutic system is evaluated under the same conditions as that outlined in Example 6. The results are shown in Table VI.

Table VI: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Indomethacin - A Non-Steroidal Anti-Arthritic Drug

TPIS*	Skin Permeation Rate (mcg/cm <sub>2</sub> /hr)		
	<u>pH 2.5</u>	<u>pH 4.5</u>	<u>pH 5.5</u>
No	-	-	1.47
Yes	0.76	0.44	6.30

\*TPIS applied a DC current of 1.2 mA periodically at 5 min/hr, for 7 hours, with a frequency of 2000 Hz, a square waveform and an on/off ratio of 2/1.

#### Example 11

An aqueous buffer solution of vasopressin (50 mcg/ml containing 1.7 mCi/ml H<sub>3</sub>-vasopressin) is prepared in citrate-phosphate buffer at pH 5.0. An aliquot of 3.5 ml of this vasopressin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permeation cell at 37°C. Samples are withdrawn at regular intervals and radioactivity is measured by scintillation counter to determine the amount of vasopressin which has been transdermally absorbed.

5           The results demonstrate that vasopressin permeates  
through the hairless rat skin at constant, but slow rate for  
10       30 hours ( $0.94 \pm 0.62$  ng/cm<sub>2</sub>/hr) (FIG. 22).

15           When the skin is treated with transdermal periodic  
iontophoretic system (TPIS) at current intensity of 0.5 and  
1mA, frequency of 2 KHz, on/off ratio of 1/1, and at the  
rate of 10 min. per 40 min. for 4 hours, the skin permeation  
20       profiles are enhanced with rate increases from 0.94 ( $\pm 0.62$ )  
ng/cm<sub>2</sub>/hr (referred to as "passive diffusion" in FIG. 20) to  
116.2 ( $\pm 10.7$ ) and 178.0 ( $\pm 25$ ) ng/cm<sub>2</sub>/hr, respectively.  
25       After the treatment with transdermal periodic iontophoretic  
system, referred to in following Table VII as "post-activation  
30       phase," the rate of skin permeation of vasopressin is  
reduced to the basal rate of only 0.7 ( $\pm 0.4$ ) and 5.3 ( $\pm$   
0.5) ng/cm<sub>2</sub>/hr, respectively. The results of the experiment  
35       are shown in FIG. 22 and in the following Table VII.

Table VII: Effect of TPIS on Skin  
Permeation Rate of Vasopressin

No TPIS	0.0 mA	9.12 ( $\pm 1.06$ )	0.94 ( $\pm 0.62$ )
With TPIS			
a) Activation phase <sub>(2)</sub>	0.5 mA	<0.5	116.2 ( $\pm 0.4$ )
b) Post-Activation phase	0.0 mA	---	0.7 ( $\pm 0.4$ )
a) Activation phase <sub>(2)</sub>	1.0 mA	<0.5	178.0 ( $\pm 25.0$ )
b) Post-Activation phase	0.0 mA	---	5.3 ( $\pm 0.5$ )

1) In-vitro permeation across hairless rat skin mounted in the Valia-Chien permeation cell.

2) Application of DC at on/off ratio of 1/1 and frequency of 2 KHz, by multi-channel TPIS unit (shown in FIG. 22 for 10 min. per 40 minute period, treatment repeated for six 40-minute cycles.

#### Example 12

An aqueous solution of insulin (5.3 IU/ml containing 0.3 mCi of I<sub>125</sub>-insulin) is prepared and adjusted to pH 7.1 using NaOH. An aliquot of 3.5 ml of this insulin solution is filled into the refillable dosage unit having a micro-porous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permea-

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tion cell at 37°C. Samples are withdrawn at regular time intervals and radioactivity is measured by scintillation counter to determine the amount of insulin which has been transdermally absorbed.

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The results demonstrate that insulin permeates through the hairless rat skin at constant, but at a slow rate for 48 hours ( $3.94 \pm 0.29$  mcIU/cm<sub>2</sub>/hr) (FIG. 23A).

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When the skin is treated with transdermal therapeutic system (TIDD) at current intensity of 1mA, frequency of 0 Hz, on/off ratio of 1/1, and at the rate of 5 min. per 60 min. for 7 hours, the skin permeation profiles are enhanced with rate increased from 3.94 ( $\pm 0.29$ ) mcIU/cm<sub>2</sub>/hr to 37.5 ( $\pm 4.5$ ) mcIU/cm<sub>2</sub>/hr. FIG. 23B shows comparison of insulin permeation data in FIG. 23A using no iontotherapy (0) over a 7-hr. period with permeation data of same insulin solution using TIDD iontotherapy.

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#### Example 13

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An aqueous solution of insulin (5.3 IU/ml containing 0.3 mCi of I<sub>125</sub>-insulin) is prepared and adjusted to pH 3.7, 5.2 or 7.1 using either HCl or NaOH solution. An aliquot of 3.5 ml of this insulin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface

5       thereof is applied to the stratum corneum side of hairless  
10       rat skin mounted in the Valia-Chien skin permeation cell at  
      37°C. Samples are withdrawn at regular time intervals and  
      radioactivity is measured by scintillation counter to deter-  
15       mine the amount of insulin which has been transdermally  
      absorbed.

      The results demonstrate that insulin permeates through  
20       the hairless rat skin at constant, but at a slow rate for 48  
      hours, with permeability coefficient ranging from 6.50  
      (+4.2) to 10.02 (+1.94)  $\times 10^{-7}$  cm/hr (Table VIII).  
25       Permeability coefficient is the ratio of the steady state  
      rate of skin permeation of the pharmaceutical which is  
30       transdermally absorbed/the concentration of the pharmaceu-  
      tical solution which is applied transdermally. The pharmaceu-  
      tical in this experiment is insulin.

35       When the skin is treated with transdermal therapeutic  
      system (TIDD) at current intensity of 1mA, frequency of 0  
40       Hz, on/off ratio of 1/1, and at the rate of 5 min. per 60  
      min. for 7 hours, the skin permeation profiles are enhanced  
      with skin permeability coefficient increased to a range from  
45       70.76 (+8.56)  $\times 10^{-7}$  to 242.59 (+18.43)  $\times 10^{-7}$  cm/hr, which  
      show dependence on solution pH. The lower pH solution (pH  
50       3.7) shows greater increase in TPIS-facilitated skin per-  
      meability.

5 Table VIII: Skin Permeability Coefficient of Insulin  
(Hairless Rats)

10	Donor Solution	Permeability Coefficient <sup>(1)</sup> (cm/hr $\pm$ SE) $\times 10$	
	<u>pH</u>	<u>No TIDD</u>	<u>With TIDD</u>
15	3.7	6.50 ( $\pm 1.42$ )	242.59 ( $\pm 18.43$ )
	5.2	10.02 ( $\pm 1.94$ )	120.07 ( $\pm 22.86$ )
	7.1	7.43 ( $\pm 0.54$ )	70.76 ( $\pm 8.56$ )

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(1) Triplicate Determinations

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#### Example 14

30 An aqueous buffer solution of insulin (250 IU/ml) is prepared in citrate-phosphate buffer at pH 3.68. An aliquot of 2.5 ml of this insulin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the skin at abdominal region of 3 groups of anesthetized, diabetic hairless rats. Blood samples are withdrawn at regular time intervals and glucose levels are measured by glucose analyzer. The reduction in glucose level from hyperglycemic state is the pharmacodynamic response to the insulin absorbed transdermally. The results demonstrate that when the skin is treated with transdermal periodic iontophoretic system (TPIS) at current intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1, for 40 min.

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5 the blood glucose levels are reduced substantially. The  
10 data show that the time course and the extent of reduction  
in blood glucose levels in diabetic rats vary with the type  
of waveform used (FIG. 24).

15  
Example 15

20 An aqueous buffer solution of insulin (250 IU/ml) is  
prepared in citrate-phosphate buffer at pH 3.68. An aliquot  
25 of 2.5 ml of this insulin solution is filled into the  
refillable dosage unit having a microporous membrane as the  
drug-releasing surface. The dosage unit is then assembled  
30 as a part of the pharmaceutical reservoir electrode of the  
iontotherapeutic device and membrane surface thereof is  
applied to the skin at abdominal region of 5 anesthetized,  
35 diabetic hairless rats. Blood samples are withdrawn at  
regular time intervals and glucose levels are measured by  
glucose analyzer. The reduction in glucose level from  
40 hyperglycemic state is the pharmacodynamic response to the  
insulin absorbed transdermally. The results demonstrate  
45 that when the skin is treated on Day 1 with transdermal  
periodic iontophoretic system (TPIS) with insulin in the  
pharmaceutical reservoir electrode at current intensity of 1  
50 mA, frequency of 2 KHz, square waveform, on/off ratio of  
1/1, for 40 min. the blood glucose levels are reduced sub-  
55 stantially (FIG. 25A). On Day 3, the diabetic rats are  
treated again with TPIS with no insulin in the pharmaceuti-

5 cal reservoir electrode (placebo formulation), the blood  
glucose is also reduced, indicating that part of the insulin  
10 delivered transdermally on Day 1 forms a depot in the skin  
tissue and can be triggered to be systemically absorbed on  
Day 3 (FIG. 25B).

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Example 16

20 An aqueous buffer solution of insulin (500 IU/ml) at pH  
7.10 is used. An aliquot of 2.5 ml of this insulin solution  
is filled into the refillable dosage unit having a micro-  
25 porous membrane as the drug-releasing surface. The dosage  
unit is then assembled as a part of the pharmaceutical  
30 reservoir electrode of the iontotherapeutic device and mem-  
brane surface thereof is applied to the skin at dorsal  
region of 3 diabetic rabbits. Blood samples are withdrawn  
35 at regular time intervals and analyzed for immunoreactive  
insulin concentration by radioimmunoassay and for glucose  
40 levels by glucose analyzer. The reduction in glucose level  
from hyperglycemic state is the pharmacodynamic response to  
the insulin absorbed transdermally. The results demonstrate  
45 that when the skin is treated with transdermal periodic  
iontophoretic system (TPIS) at current intensity of 1 mA,  
50 frequency of 2 KHz, on/off ratio of 1/1, and square waveform  
for 40 min. the plasma immunoreactive insulin concentration  
increases rapidly and the blood glucose levels are reduced  
55 substantially. The plasma insulin profile (FIG. 26A) as  
well as the time course and the extent of reduction in blood

5 glucose levels (FIG. 26B) in diabetic rabbits are compared  
with the results from the conventional subcutaneous adminis-  
10 tration of insulin. The data show that plasma insulin con-  
centrations as well as blood glucose levels can be effec-  
15 tively controlled using TPIS system of this invention. FIG.  
24B shows that by using the TPIS system of this invention  
the blood glucose level (B.G.L.) can be appropriately  
20 reduced in a more controlled manner than by daily SC dosages  
so as to prevent B.G.L. to fall below normal levels.

25 Example 17

30 An aqueous buffer solution of insulin (500 IU/ml) at pH  
7.10 is used. An aliquot of 2.5 ml of this insulin solution  
is filled into the refillable dosage unit having a micro-  
35 porous membrane as the drug-releasing surface. The dosage  
unit is then assembled as a part of the pharmaceutical  
reservoir electrode of the iontotherapeutic device and mem-  
40 brane surface thereof is applied to the skin to the  
abdominal skin of 2 groups of diabetic rabbits. Blood  
45 samples are withdrawn at regular time intervals and analyzed  
for immunoreactive insulin concentration by radioimmunoassay  
and for glucose levels by glucose analyzer. The reduction  
50 in glucose level from hyperglycemic state is the pharmaco-  
dynamic response to the insulin absorbed transdermally.  
55 The results demonstrate that when the skin is treated with  
transdermal periodic iontophoretic system (TPIS) at current

5 intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1,  
and square waveform for 40 min., the plasma immunoreactive  
10 insulin concentration increases more rapidly and the blood  
glucose levels are reduced more instantaneously than trans-  
dermal iontophoretic delivery (TIDD) at current intensity of  
15 4 mA for 80 min. (FIG. 27). The data in FIGS. 25A and B  
show that the TPIS system of this invention provides both a  
20 more rapid increase in plasma insulin concentration after  
administration and a more rapid reduction in blood glucose  
level than use of TIDD even though the corresponding current  
25 intensity in the TIDD system is 4 times as much (4 mA vs. 1  
mA) and administration is 2 times as great (80 minutes vs.  
30 40 minutes) as in the TPIS system.

#### Example 18

35 An aqueous buffer solution of vasopressin (40 IU/ml) is  
prepared in citrate-phosphate buffer at pH 5.0. Vasopressin  
40 is an anti-diuretic pharmaceutical, which is used by  
patients which have an excessive urine output. Vasopressin  
caused a reduction of urine output and an increase in ion  
45 content, such as sodium ion content. Ion content in the  
urine is determined by using osmolarity measurement. An  
50 aliquot of 3.5 ml of this vasopressin solution is filled  
into the refillable dosage unit having a microporous mem-  
brane as the drug-releasing surface. The dosage unit is  
55 then assembled as a part of the pharmaceutical reservoir  
electrode of the iontotherapeutic device and membrane sur-

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face thereof is applied to the abdominal skin of 2 groups of anesthetized rabbits. Blood samples are withdrawn and urine samples are collected at regular time intervals and urine osmolarity is measured by osmometer. The increases in osmolarity from the basal level are the pharmacodynamic responses to the vasopressin transdermally absorbed.

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The results demonstrate that when the skin is treated with transdermal periodic iontophoretic system (TPIS) at current density of 0.22 mA/cm<sub>2</sub>, frequency of 2 KHz, on/off ratio of 1/1, and square waveform for 40 min., the urine osmolarity increases from the basal levels more rapidly and substantially than with transdermal iontophoretic delivery (TIDD) under the same experimental conditions (FIG. 28).

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Example 19

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An aqueous buffer solution of vasopressin (50 mcg/ml containing 1.7 mCi/ml H<sub>3</sub>-vasopressin) is prepared in citrate-phosphate buffer at pH 7.4 with varying ionic strengths. An aliquot of 3.5 ml of this vasopressin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permeation cell at 37°C. Samples are withdrawn at regular

time intervals and radioactivity is measured by scintillation counter to determine the amount of vasopressin which has been transdermally absorbed. The results demonstrate that vasopressin permeates through the hairless rat skin at constant, but slow rate for 30 hours ( $1.32 \pm 0.38$  ng/cm<sub>2</sub>/hr). When the skin is treated with transdermal periodic iontophoretic system (TPIS) at current intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1, and at the rate of 10 min. per 40 min. for 4 hours, the skin permeation profiles are enhanced with rate increases from 1.32 ( $\pm 0.38$ ) ng/cm<sub>2</sub>/hr (referred to as "passive diffusion") to the range of 65.9 ( $\pm 13.1$ ) to 632 ( $\pm 65.0$ ) ng/cm<sub>2</sub>/hr, depending upon the ionic strength of vasopressin solution. The results of the experiment are shown in the following Table IX.

Table IX: Effect of Ionic Strength on Skin Permeation Rate of Vasopressin

<u>Ionic Strength</u>	<u>Skin Permeation Rate<sub>1</sub></u> (ng/cm <sub>2</sub> /hr $\pm$ SD)	<u>Enhancement Factor<sub>2</sub></u>
0.488	65.9 ( $\pm$ 13.1)	49.9 ( $\pm$ 18.0)
0.244	101.4 ( $\pm$ 9.1)	76.8 ( $\pm$ 6.9)
0.122	244.6 ( $\pm$ 26.3)	185.3 ( $\pm$ 19.9)
0.061	632.6 ( $\pm$ 65.0)	472.8 ( $\pm$ 59.0)

<sub>1</sub>) The rates determined in the activation phase with lag time ranging from 0.48 ( $\pm$  0.21) to 0.86 ( $\pm$  0.15) hrs.

<sub>2</sub>) Compared to the skin permeation rate of vasopressin by passive diffusion (1.32 ng/cm<sub>2</sub>/hr).

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The TPIS-facilitated skin permeation rate appears to be dependent upon the ionic strength of drug solution. The lower the ionic strength, the higher the rate of skin permeation and the greater the enhancement in skin permeability (FIG. 29).

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#### Example 20

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An aqueous buffered solution of vasopressin (50 mcg/ml containing 1.7 mCi/ml  $H_3$ -vasopressin) is prepared in citrate-phosphate buffer at pH 5.0 at ionic strength of 0.064. An aliquot of 3.5 ml of this vasopressin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permeation cell at 37°C. Samples are withdrawn at regular time intervals and radioactivity is measured by scintillation counter to determine the amount of vasopressin which has been transdermally absorbed.

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The results demonstrate that vasopressin permeates through the hairless rat skin at constant, but slow rate for 30 hours ( $0.98 \pm 0.26$  ng/cm<sup>2</sup>/hr).

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5           When the skin is treated with transdermal periodic  
iontophoretic system (TPIS) at current intensity of 0.3 mA  
10 frequency of 16 KHz, on/off ratio of 1/1, for 60 min., the  
skin permeation profiles are enhanced with rate increases  
15 from 0.98 ( $\pm$  0.26) ng/cm<sub>2</sub>/hr referred to as "passive dif-  
fusion") to 757.3 ( $\pm$  53.2) ng/cm<sub>2</sub>/hr (FIG. 28), while the  
duration of time lag is reduced from 9 hours down to 0.40 ( $\pm$   
20 0.06) hours). The data in FIG. 30 demonstrate the rever-  
sibility of skin permeability that in less than 2 hours  
after the TPIS treatment, the skin permeability returns to  
25 the rate before the TPIS treatment. Then, TPIS can be  
applied again to facilitate the skin permeation of vaso-  
30 pressin.



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What is Claimed is:

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1. A lightweight, portable transdermal periodic ionto-  
therapeutic device for transdermal administration of a  
systemically-effective amount of an ionized pharmaceu-  
tical, which is adapted to be worn by a subject being  
iontotherapeutically treated, comprising

15

20

1) a DC power supply capable of providing an ionto-  
therapeutically effective and physiologically  
acceptable DC current in the range up to about  
10mA;

25

30

2) a periodic waveform generator electrically con-  
nected to the DC power supply and having inte-  
grated circuitry capable of providing a) a  
periodic waveform in the square, triangular, sinu-  
soidal, trapezoidal, or other acceptable geometric  
form or combination thereof; b) an on/off ratio of  
1/50 to 10/1; and c) a repetition frequency from  
about 10 Hz to about 50 KHz;

35

40

45

50

55

3) an output circuit electrically connected to said  
waveform generator which a) can provide a periodic  
DC current in a pre-selected waveform of said  
forms; b) monitors current intensity delivered; c)  
adjusts and maintains the current intensity within  
predetermined maximum and minimum levels and d)  
delivers the current to a reservoir electrode for

5

iontotherapeutic transdermal administration of  
said peptide pharmaceutical;

10

4) a pharmaceutical reservoir electrode which can be  
preselected to be either the cathode or the anode  
depending upon whether the ionized pharmaceutical  
is anionic or cationic; said electrode having a  
receptacle adapted to receive a unit dose of said  
peptide pharmaceutical in which said peptide is in  
aqueous solution at a pH at least 1.0 pH unit  
below or above the isoelectric point of said pep-  
tide; said electrode with said received unit dose  
adapted to be placed in electrical contact with  
the intact skin to be treated iontotherapeuti-  
cally; said electrode having a terminal to receive  
and to transmit through said unit dose the said  
periodic DC current and said unit dose adapted to  
be in electrical contact with said terminal;

40

5) receptor electrode adapted to be in electrical  
contact with the intact skin to be treated and  
forming with said pharmaceutical reservoir elec-  
trode a combination of anode and cathode elec-  
trodes;

45

50

said electrodes electrically connected to said  
output circuit and providing when placed upon the

55

5 skin of a subject being treated a current path  
through the intervening tissue of the subject  
10 being treated; and

15 6) a preprogramable control element electrically  
integrated within said device to preprogram and to  
control said iontotherapeutic administration on an  
20 automated basis as in accordance with a physi-  
cian's prescription entered into the control ele-  
ment, without interaction of a subject being  
25 treated with said device for the administration  
except to permit said subject to stop operation of  
the device as in the event of an emergency.

30 2. A device of Claim 1 which has electrically connected  
with the control element thereof a sensor.

35 3. A device of Claim 2 wherein the sensor senses a level  
of a physiological entity in the body of the subject  
40 which correlates with the pharmaceutical being admin-  
istered iontothereapeutically and signals said informa-  
45 tion to said control element.

50 4. A device of Claim 2 wherein the sensor senses a pre-  
determined skin condition of the body of the subject  
and signals the information to said control element.

55

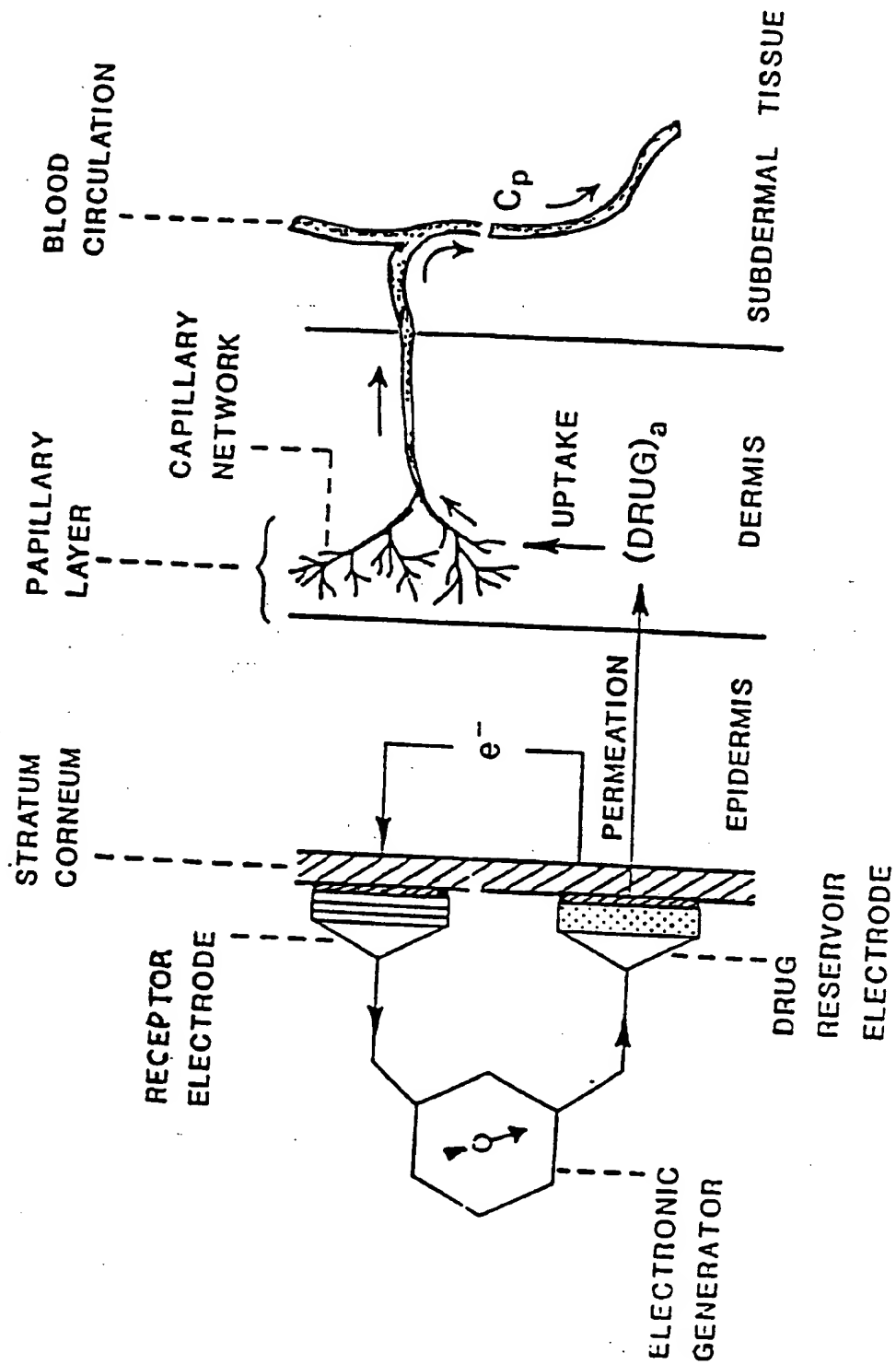
- 5           5.    A device of Claim 1 wherein the device interfaces with  
10           a computer system to enter into the control element  
          thereof a preprogrammed prescription and other instruc-  
          tions or to receive data on the functioning of the  
15           device.
- 20           6.    A device of Claim 1 wherein the device is a wrist-band  
          type.
- 25           7.    A transdermal periodic iontotherapeutic process for  
          administering a controlled and systemically effective  
30           amount of an ionized pharmaceutical which is stable for  
          transdermal administration and is transdermally absorb-  
          able using a device as defined in Claim 1, by
- 35           1)    entering a prescription or other instructions for  
          administering said pharmaceutical into the control  
          element of said device;
- 40           2)    assembling a dosage unit containing a pharmaceuti-  
          cally acceptable aqueous solution of said ionized  
45           pharmaceutical into a receptacle of a reservoir  
          electrode of said device, which electrode is a  
50           cathode or anode depending upon whether said  
          ionized peptide is anionic or cationic, said solu-  
          tion having a pH at least about 1.0 pH unit below  
55           or above the isoelectric or pKa point of said  
          pharmaceutical;

- 5                    3)    placing the cathode and anode electrodes of said  
transdermal periodic iontotherapeutic system in  
10                   electrical contact with the intact skin to be  
treated;
- 15                   4)    applying upon command of said control element an  
iontotherapeutically effective, periodic DC cur-  
20                   rent of up to about 10 mA based on a reservoir  
electrode/skin-contacting area of about 5 cm<sub>2</sub>  
using a) a periodic waveform in the square, tri-  
25                   angular, sinusoidal, trapezoidal, or other accept-  
able geometric form, or combinations thereof, b) a  
30                   physiologically acceptable repetition frequency of  
at least about 10 HZ, and c) an on/off ratio of  
from 1/50 to 10/1; said process providing a sys-  
35                   temically effective absorption of said ionized  
pharmaceutical from said solution at a rate of at  
40                   least 500 percent from that provided by passive  
diffusion transdermal absorption from said solu-  
45                   tion during an administration time of at least 2  
hours.
- 50                   8.    A process of Claim 7 wherein the ionized pharmaceutical  
is an ionized peptide pharmaceutical.

- 5           9.    A process of Claim 7 in which the pH of the pharmaceu-  
             tical solution is at least about 1.5 pH units below or  
10           above the isoelectric or pKa point of said pharmaceuti-  
             cal.
- 15           10. A process of Claim 7 in which the pH of the pharmaceu-  
             tical solution is at least about 2.0 pH units below or  
20           above the isoelectric or pKa point of said pharmaceuti-  
             cal.
- 25           11. A process of Claim 7 in which the pH of the pharmaceu-  
             tical solution is at least about 1.5 or about 1.0 pH  
30           units below the isoelectric or pKa point of said phar-  
             maceutical.
- 35           12. A process of Claim 7 in which the ionized pharmaceuti-  
             cal is insulin and the pH of the insulin solution is in  
             the range of about pH 3.0 to pH 4.0.
- 40           13. A process of Claim 7 in which the pH of the insulin  
             solution is about pH 3.6.
- 45           14. A process of Claim 7 in which the current intensity is  
             not more than about 5 mA based on a reservoir elec-  
50           trode/skin-contacting area of about 5 cm<sub>2</sub>.
- 55           15. A process of Claim 7 in which the current intensity is  
             not more than about 2 mA based on a reservoir elec-  
             trode/skin-contacting area of about 5 cm<sub>2</sub>.

- 5           16. A process of Claim 1 in which the current intensity is  
not more than 1 mA based on a reservoir electrode skin-  
10           contacting area of about 5 cm<sub>2</sub>.
- 15           17. A process of Claim 7 wherein the solution is an insulin  
solution having a pH which is at least about 1.5 pH  
units lower or higher than the isoelectric point of the  
20           insulin, the current intensity not more than about 2 mA  
based on a reservoir electrode skin-contacting surface  
area of about 5 cm<sub>2</sub>, the administration times are not  
25           more than about 40 minutes, and the repetition fre-  
quency is at least about 1000 Hz.
- 30           18. A battery belt adapted to be worn around the wrist or  
other part of a subject's body to power an electronic  
device used by said subject, said device comprising  
35           1) a band adapted to house batteries;  
2) said batteries connected in series;  
40           3) a terminal electrically connected with the series  
of batteries adapted to connect electrically  
through a connecting line with said electronic  
45           device.
- 50           19. A battery belt of Claim 18 adapted for use with a  
device of Claim 1.

FIG. 1





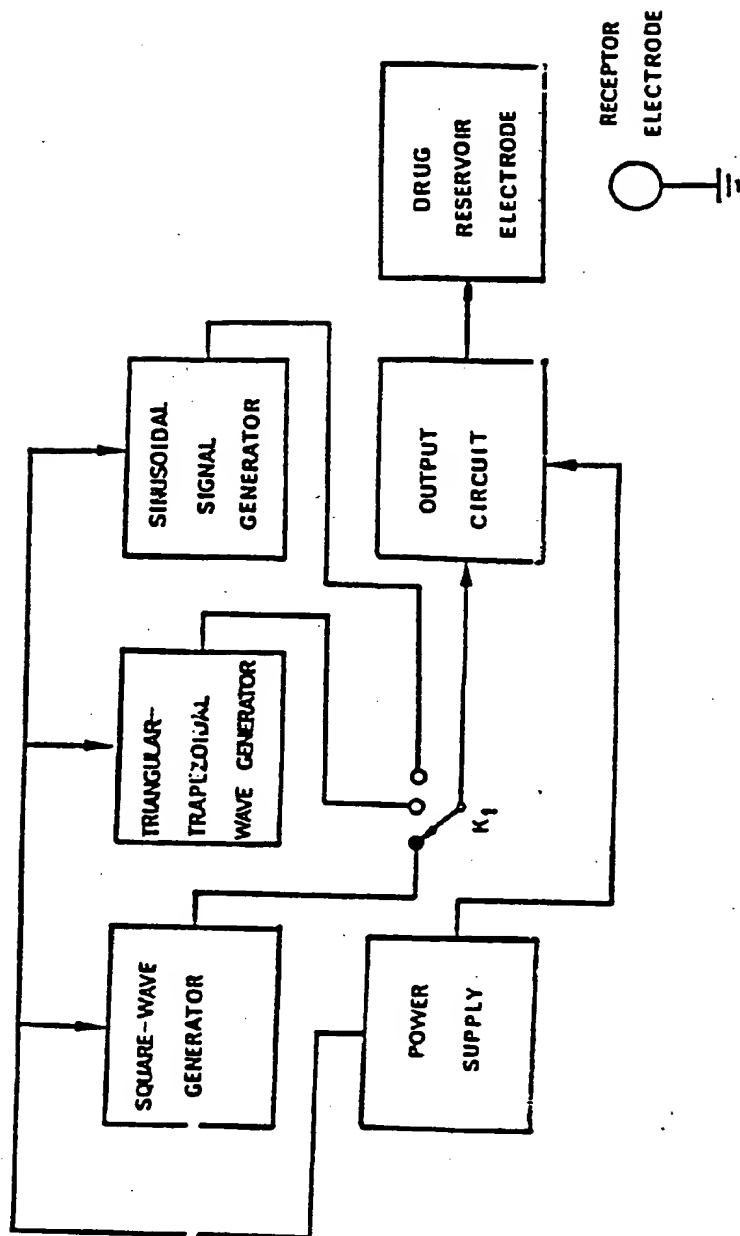


FIG. 2

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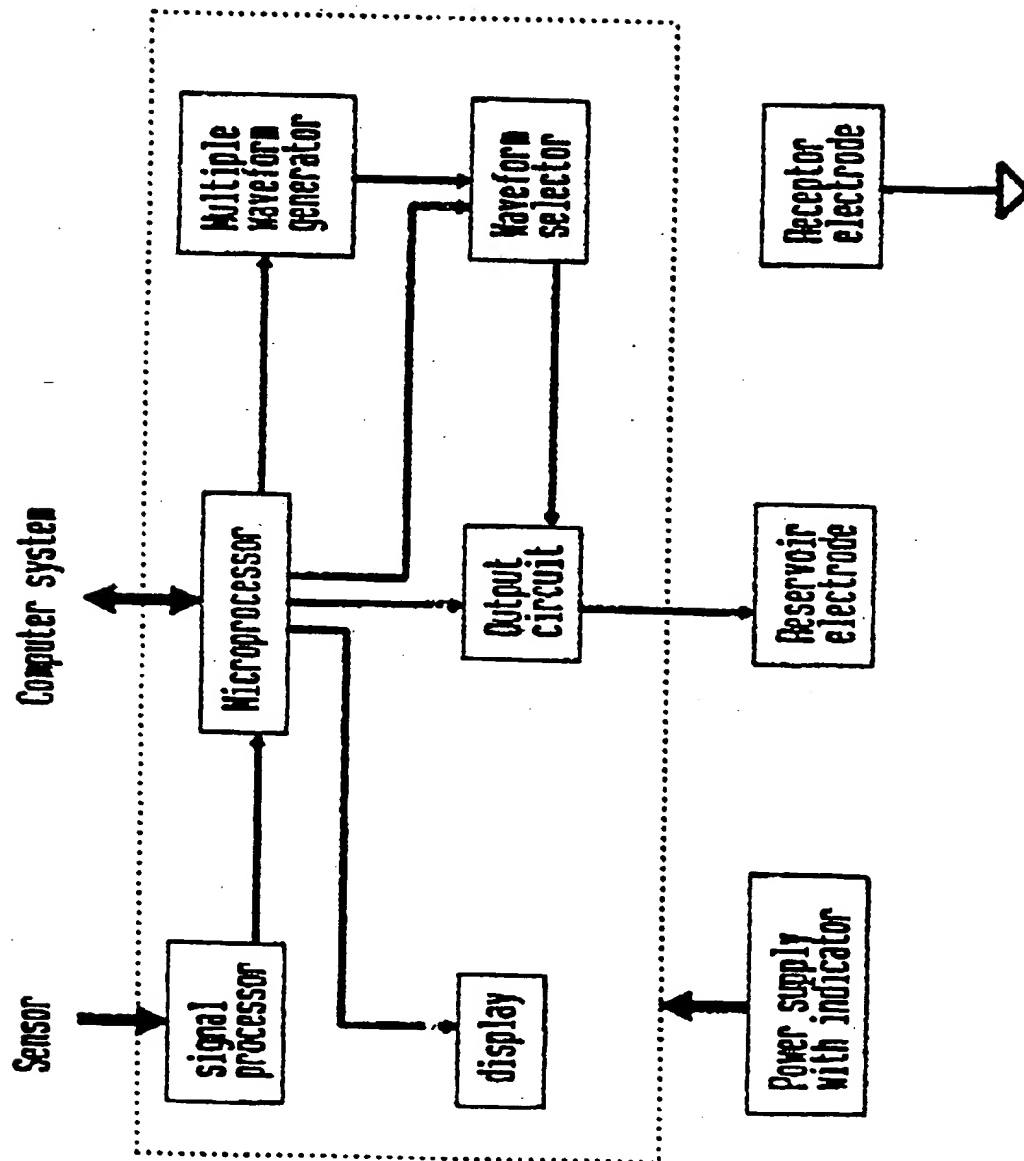


Fig. 3

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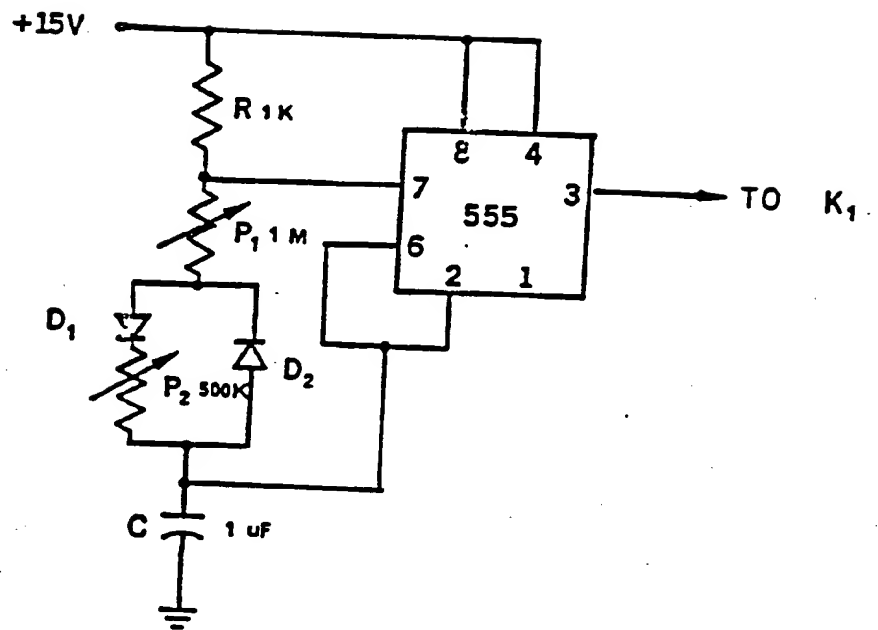


FIG. 4

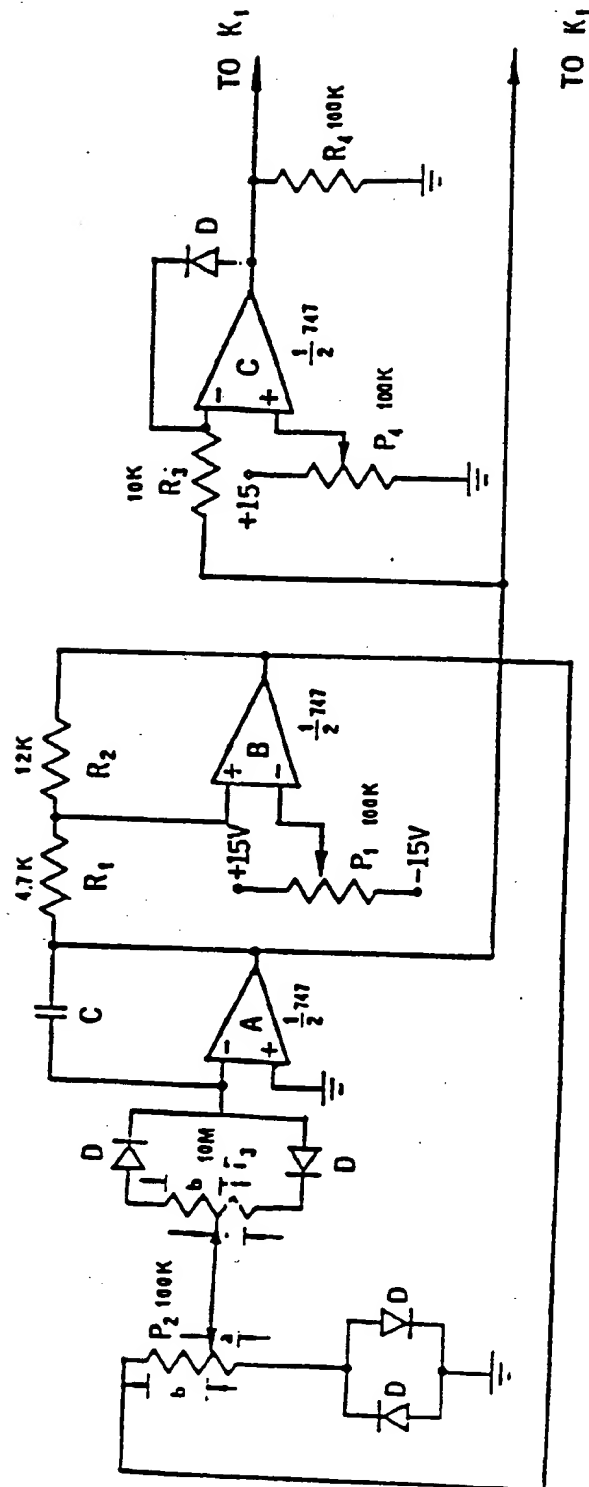


FIG. 5

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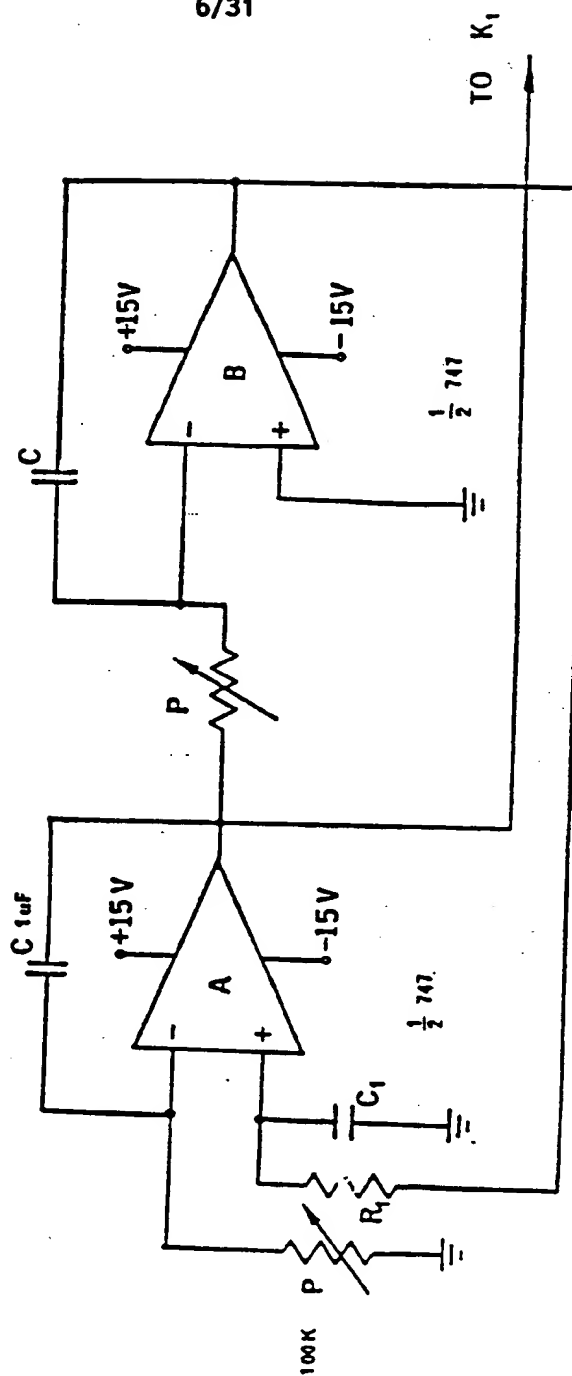


FIG. 6

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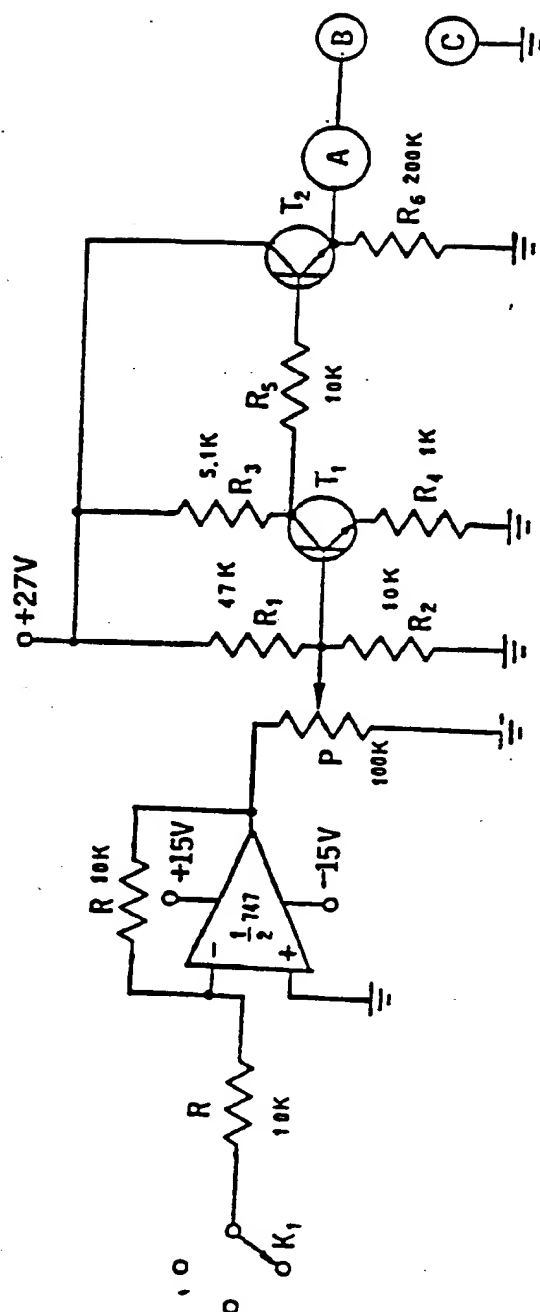


FIG. 7

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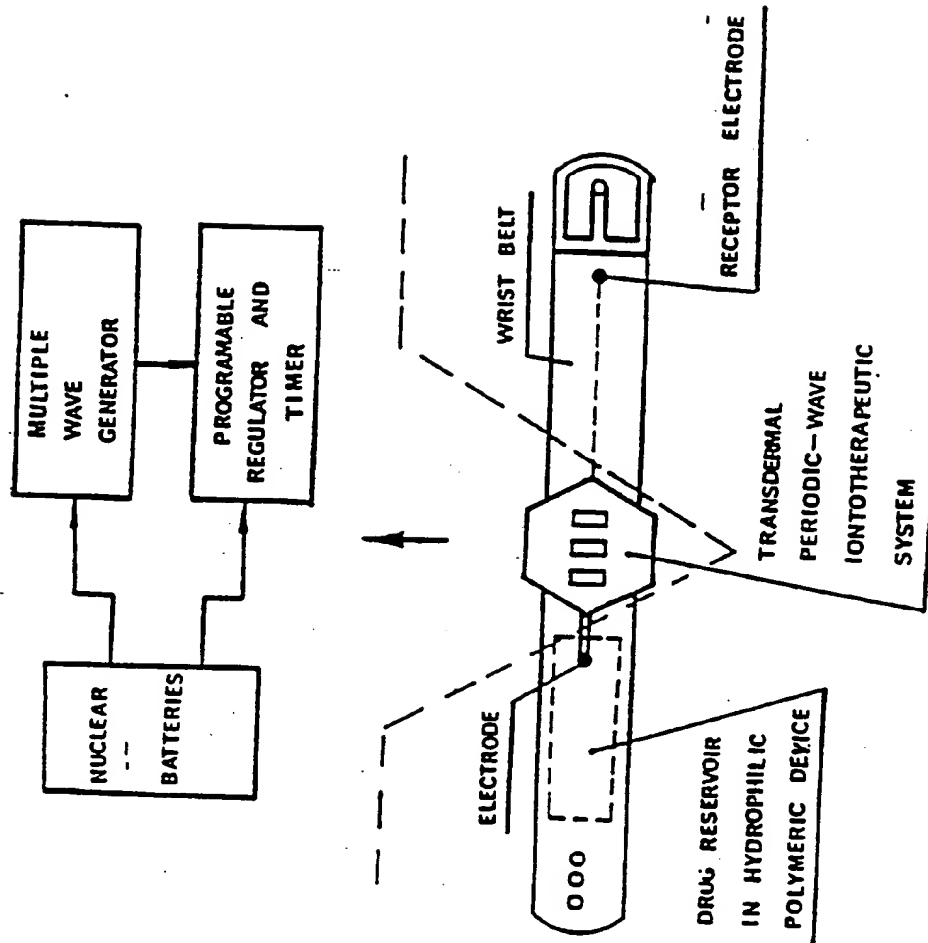


FIG. 8

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TRANSDERMAL PERIODIC IONTO-THERAPEUTIC SYSTEM  
( TPIS )

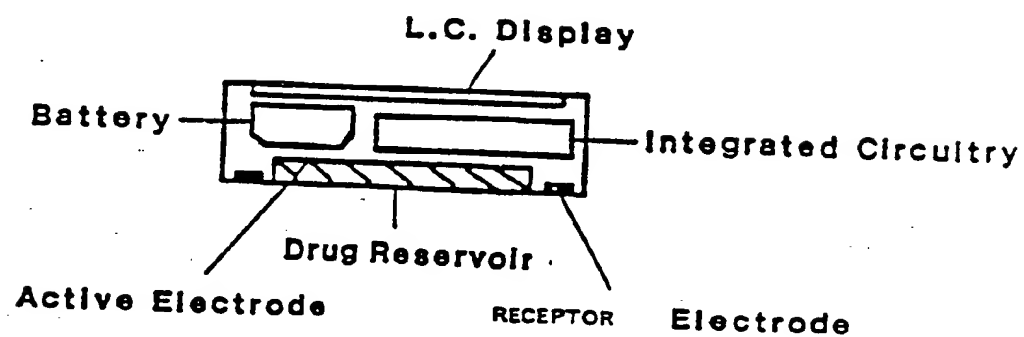


FIG. 9A

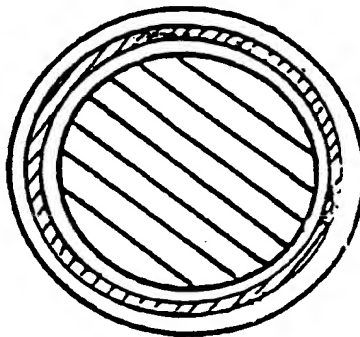


FIG. 9B



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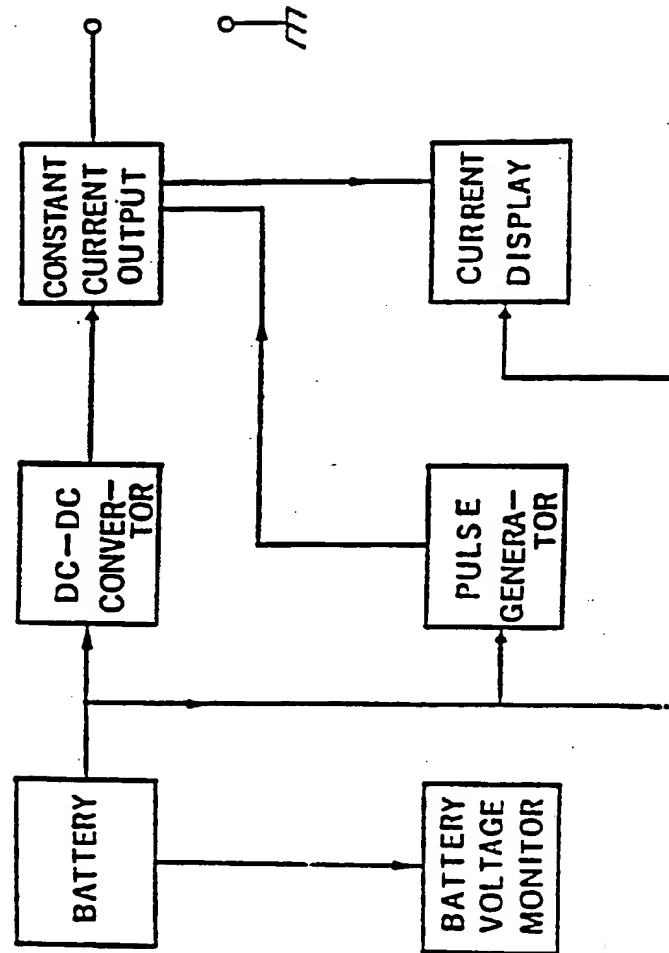


FIG. 10

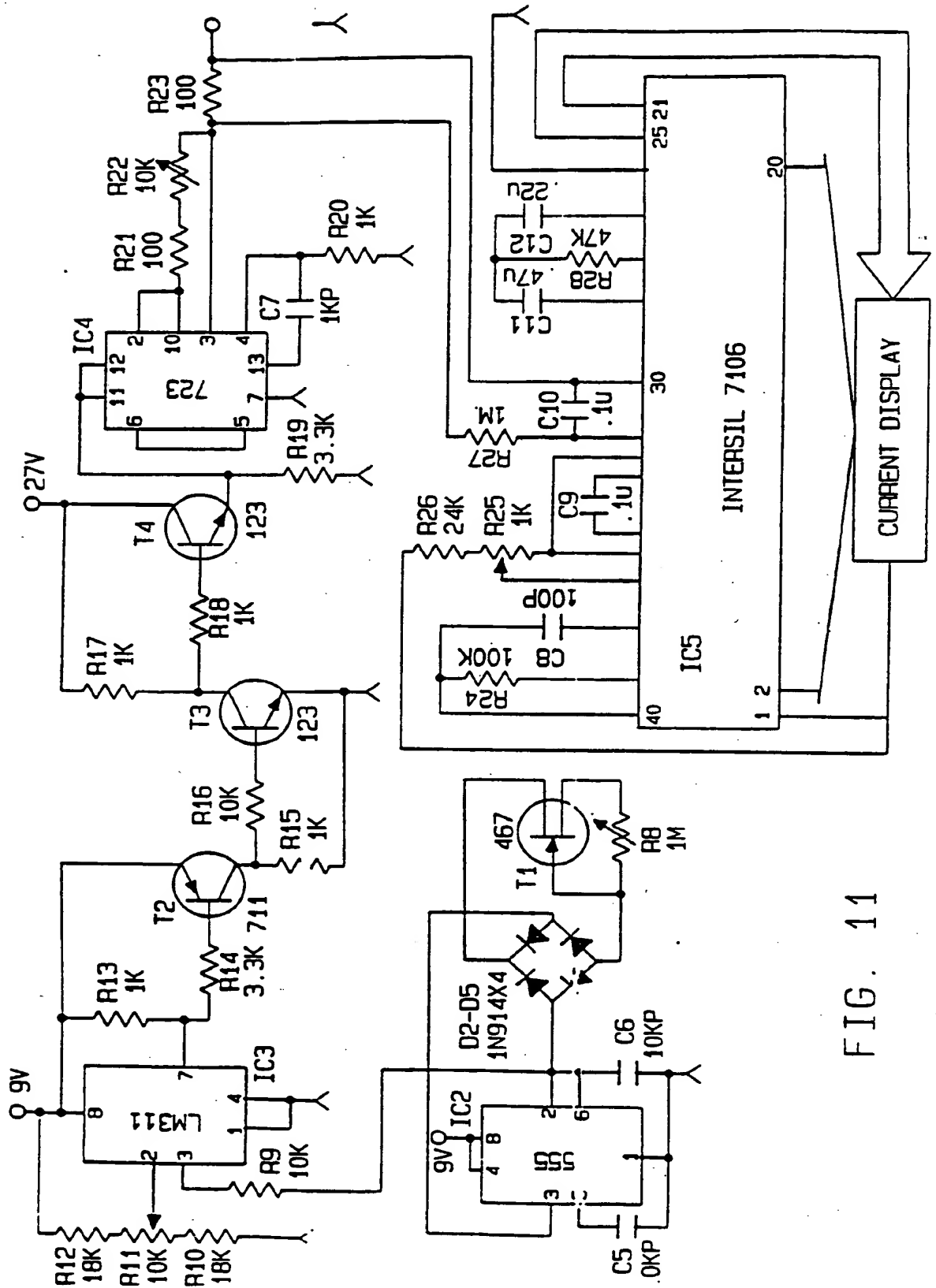


FIG. 11

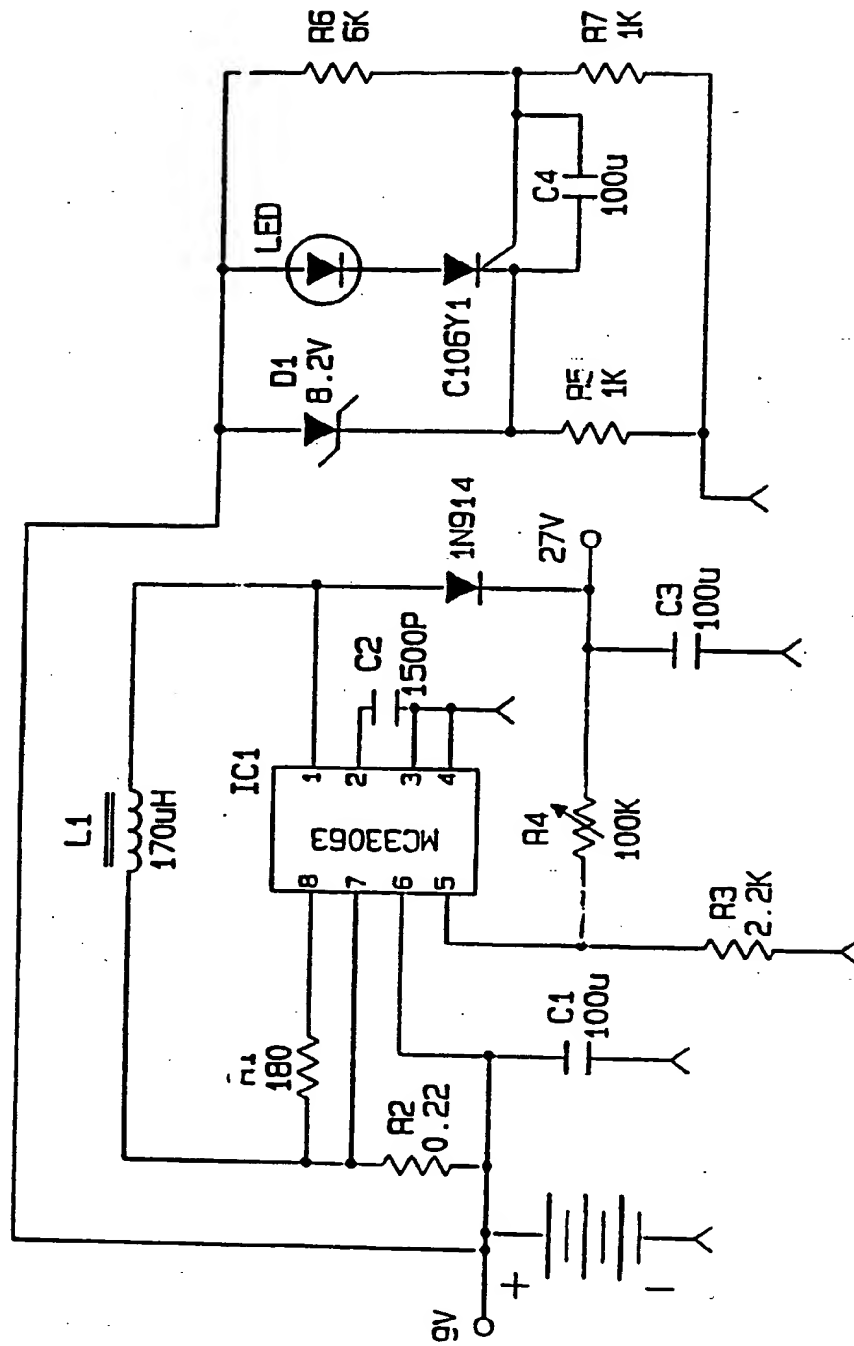
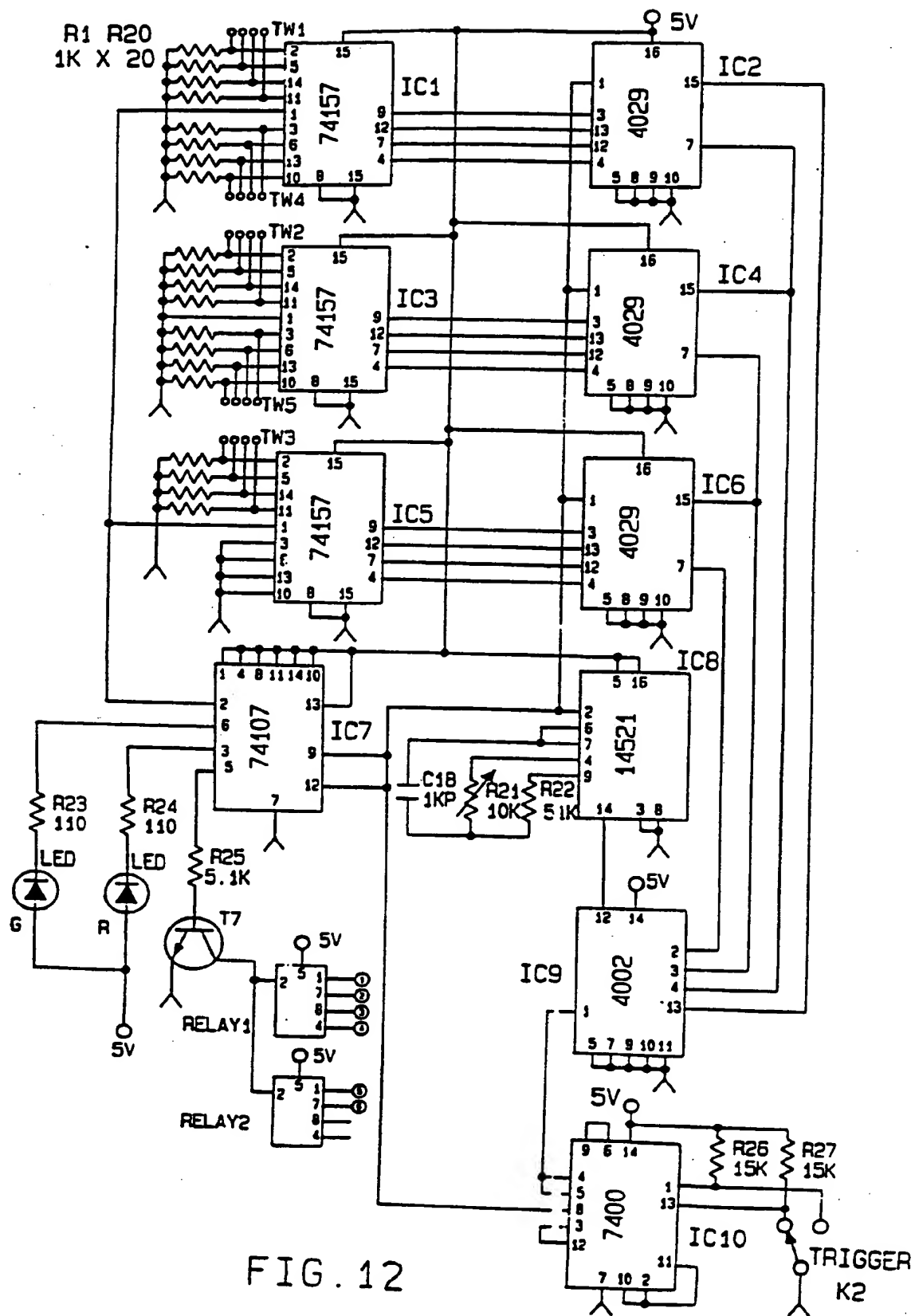


FIG. 11A



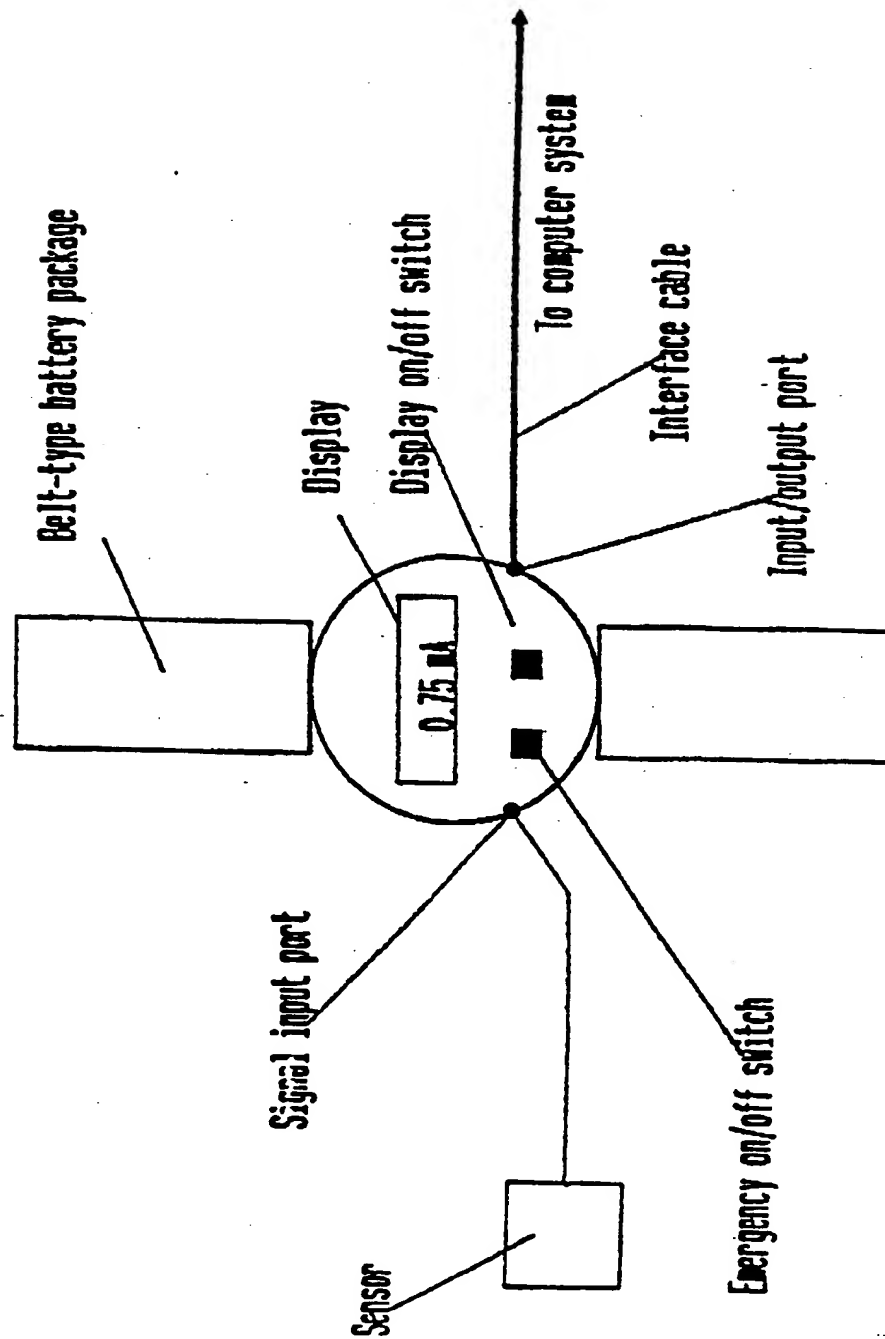


Fig. 13

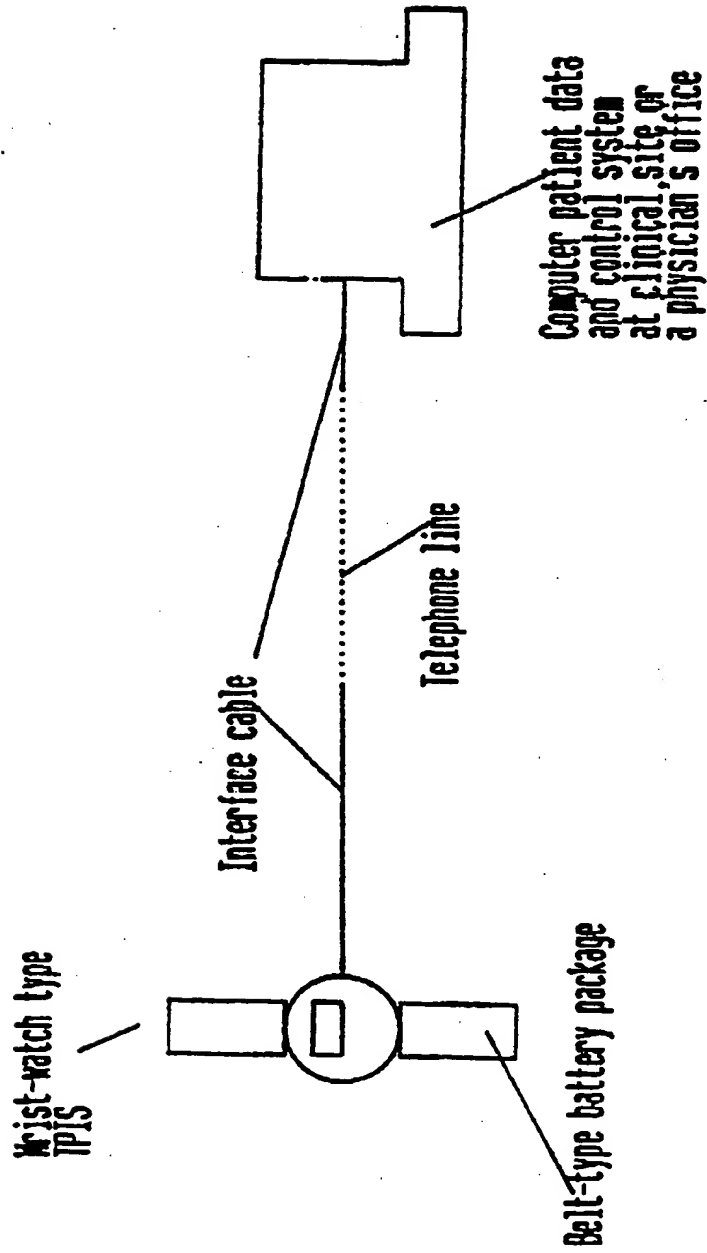


Fig. 14

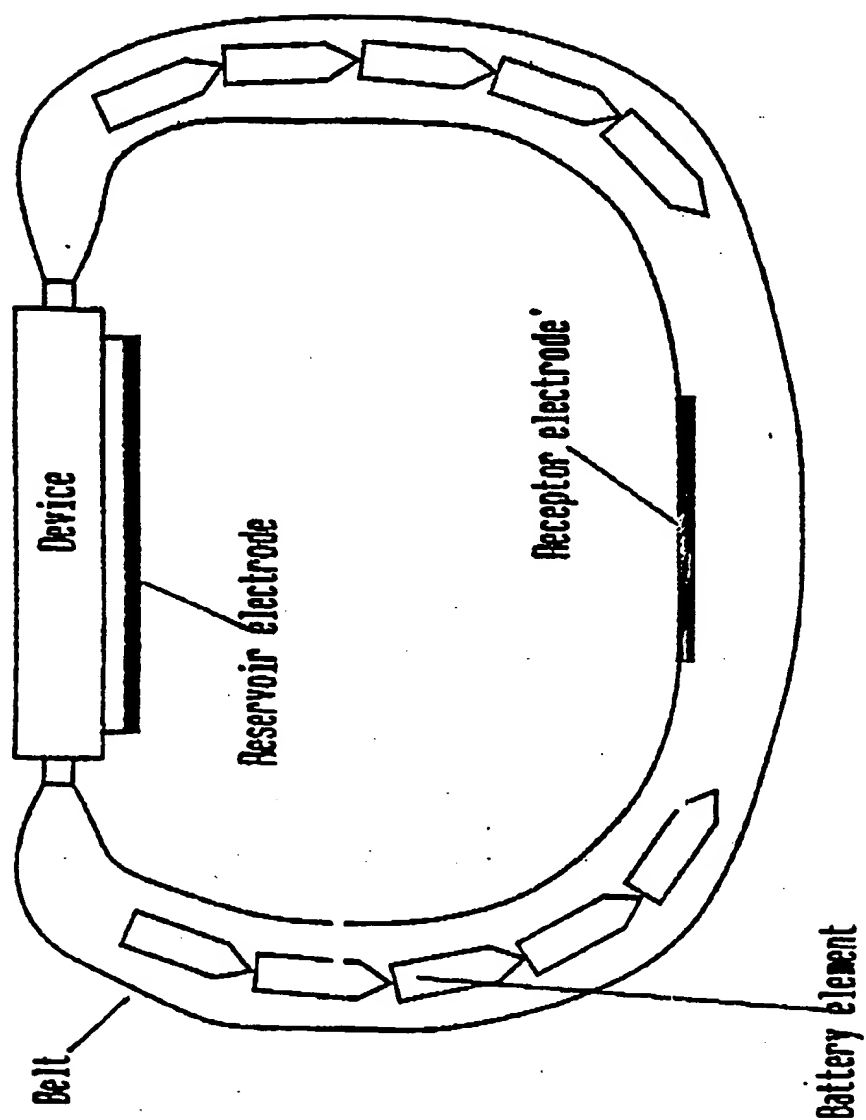


Fig. 15

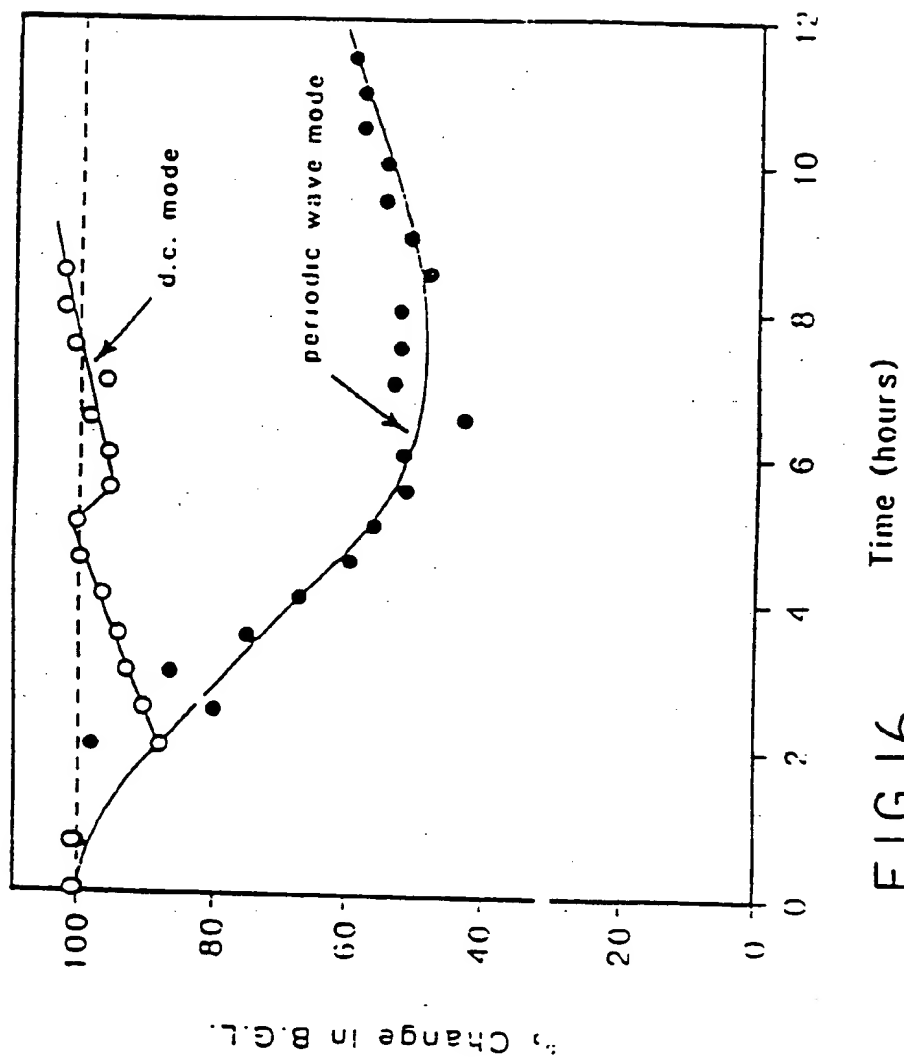
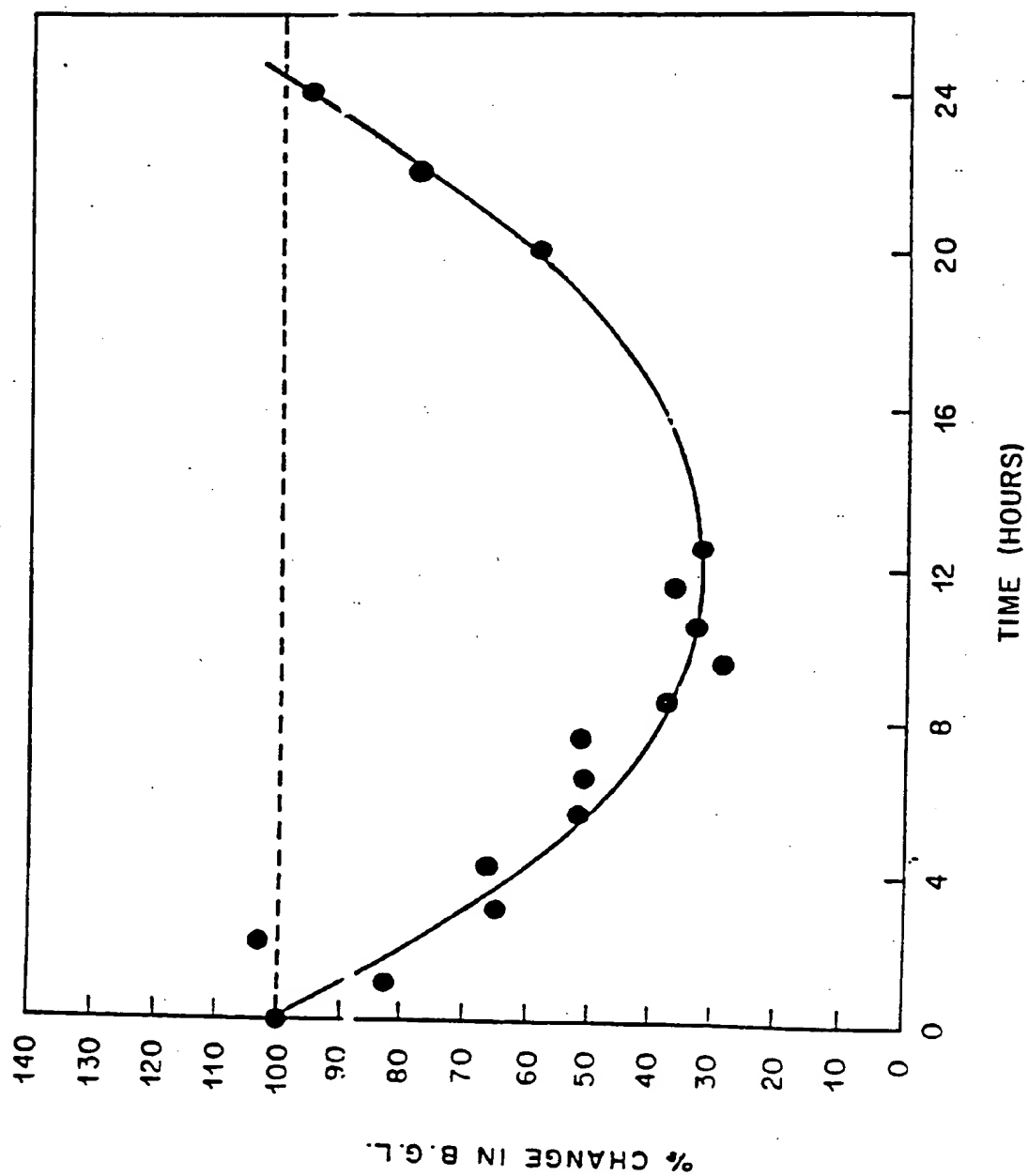


FIG. 16



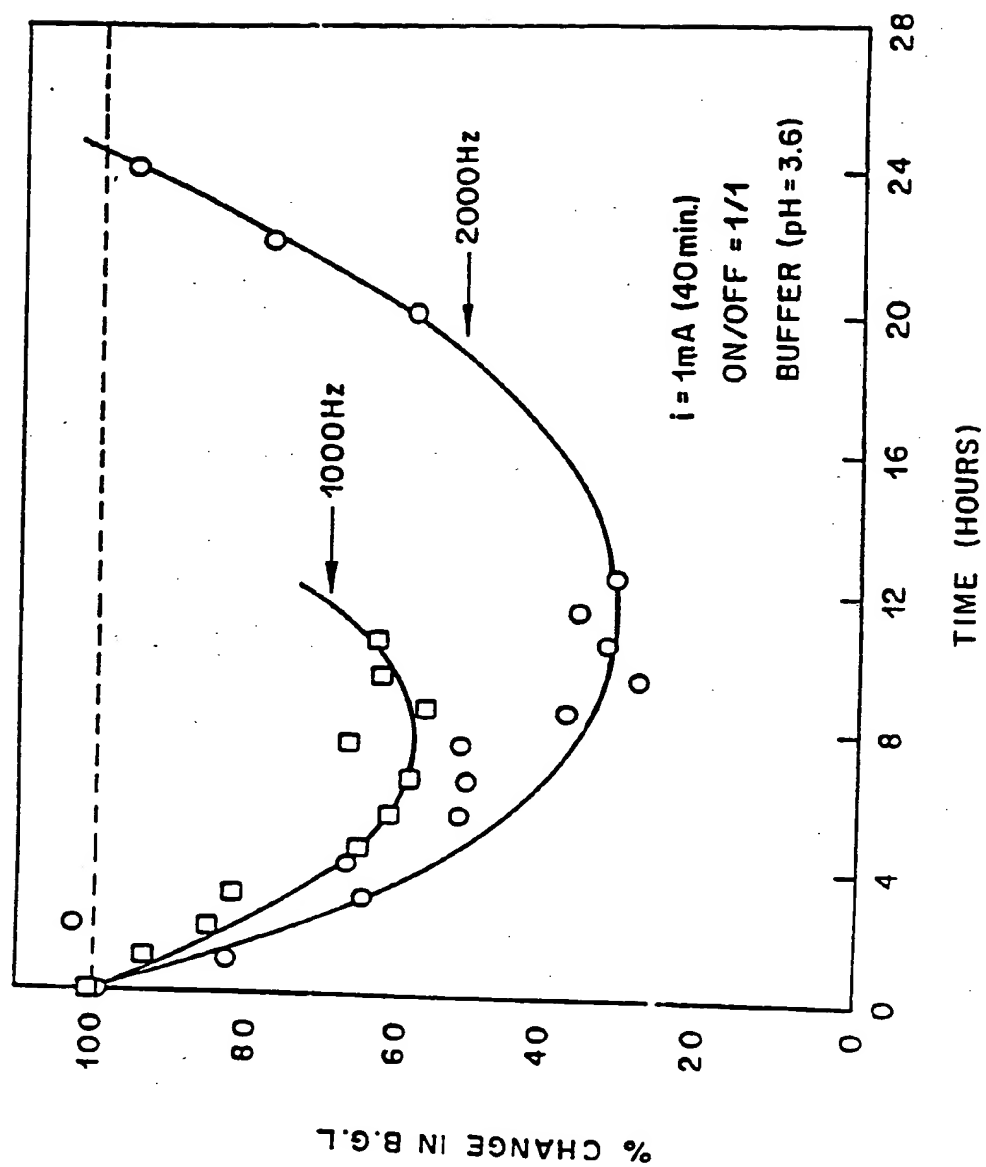
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FIG. 17



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FIG. 18



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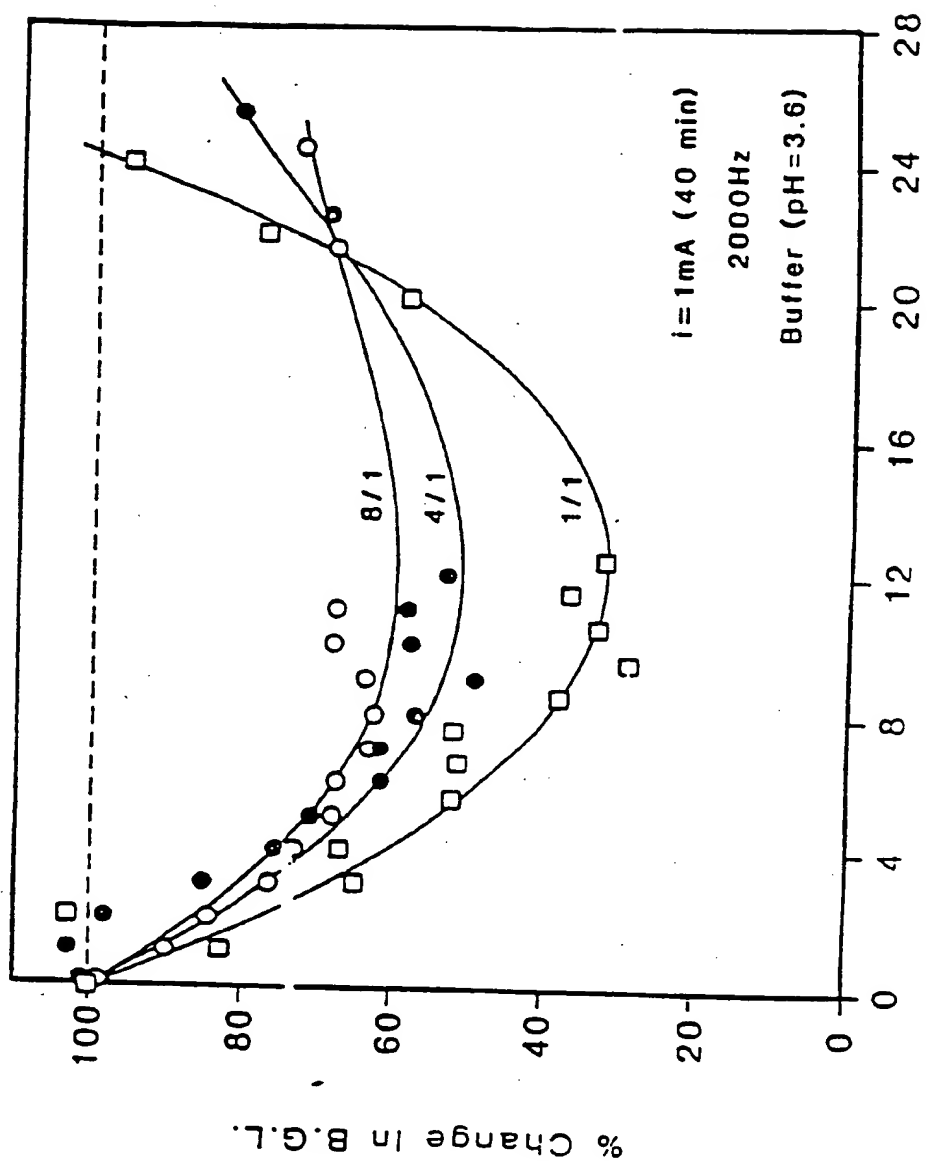
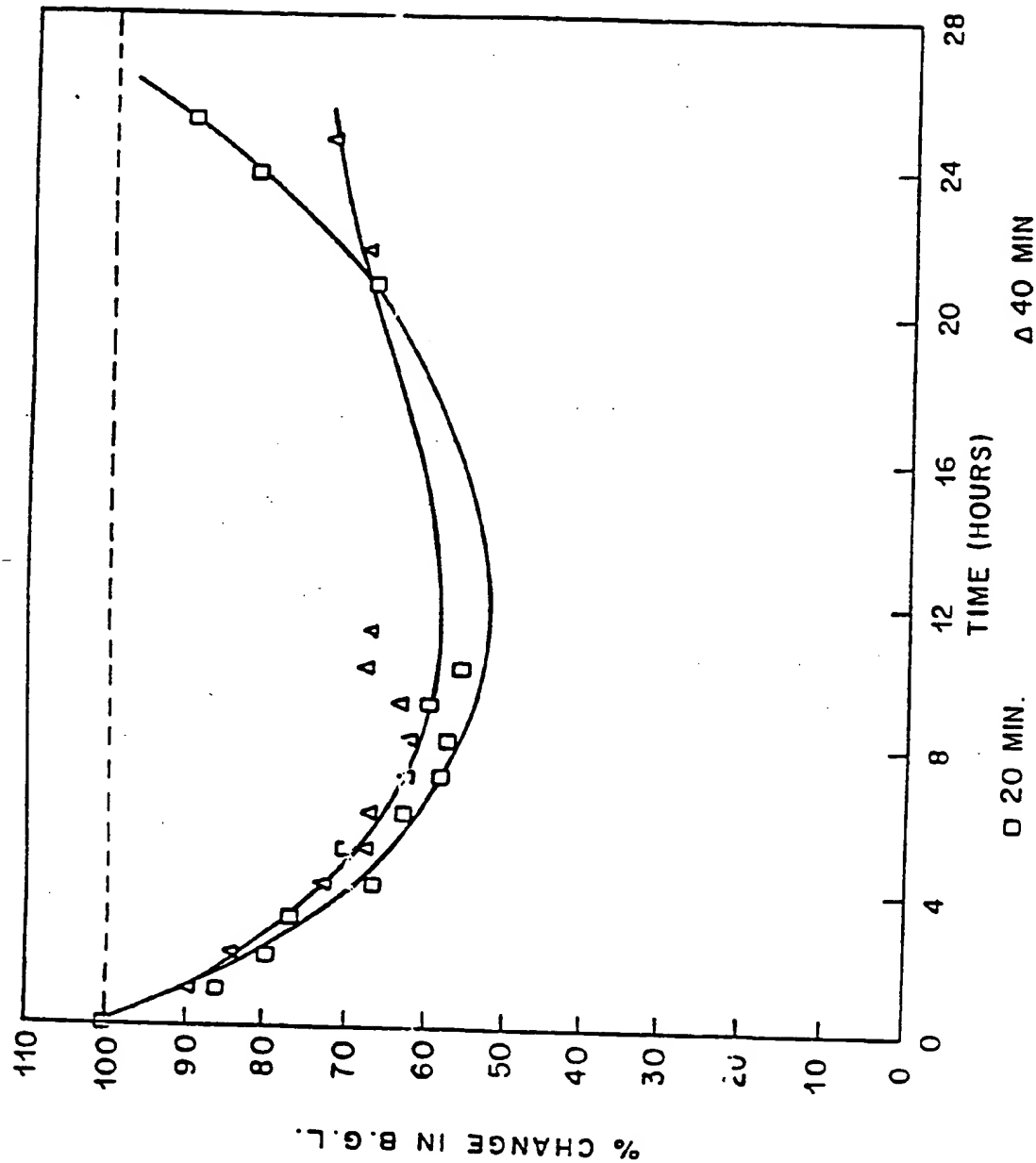


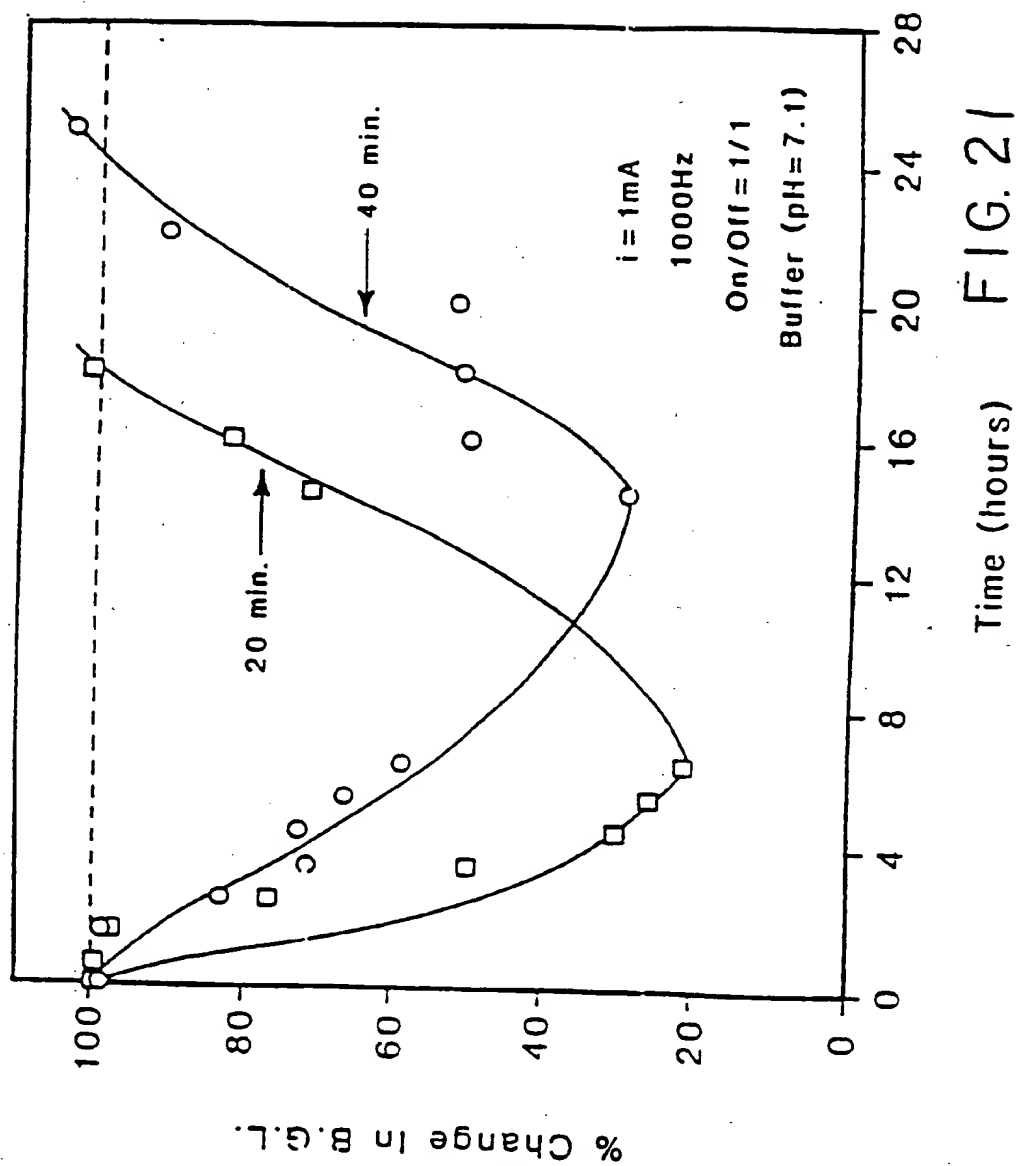
FIG. 19

Time (hours)

FIG. 20



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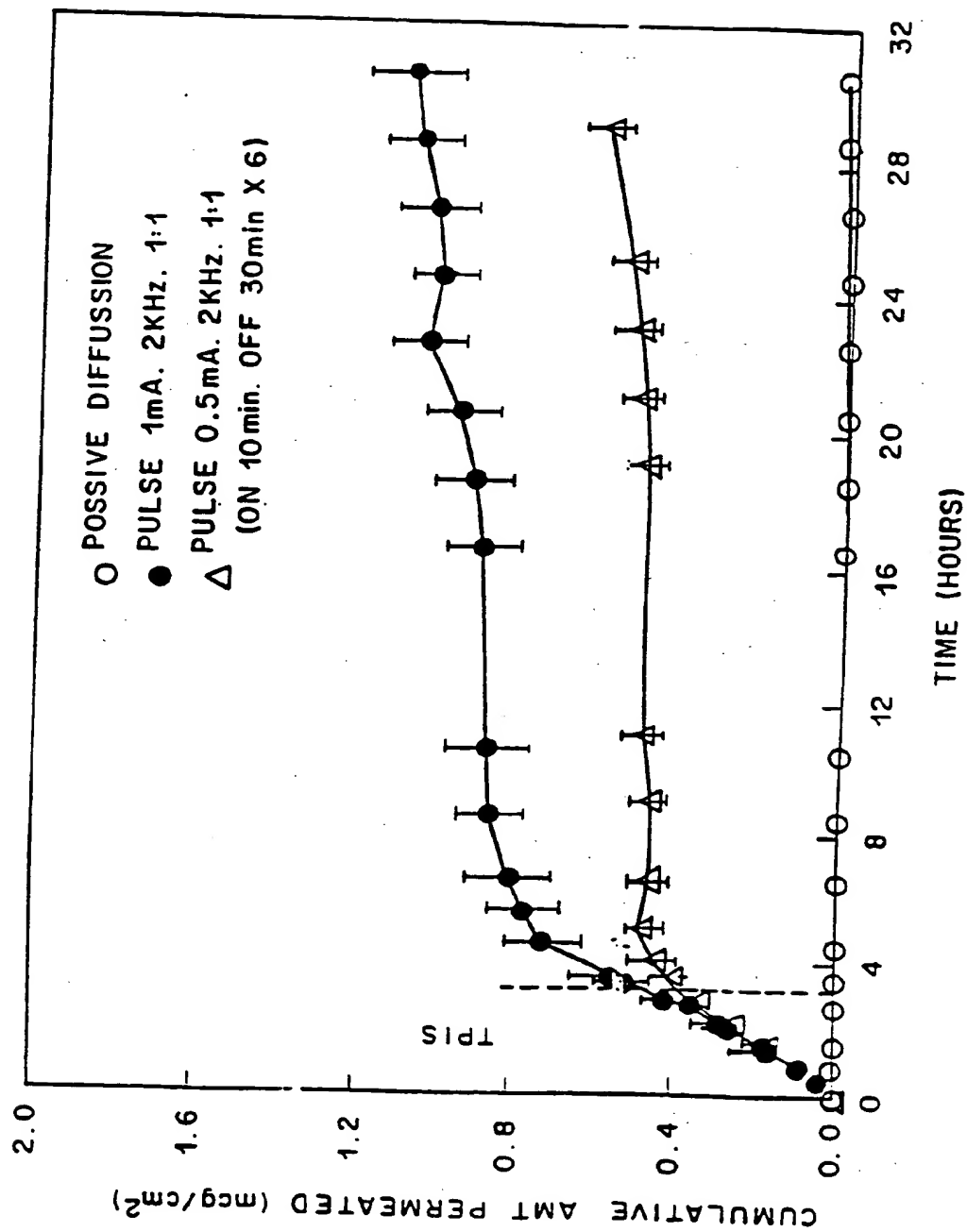
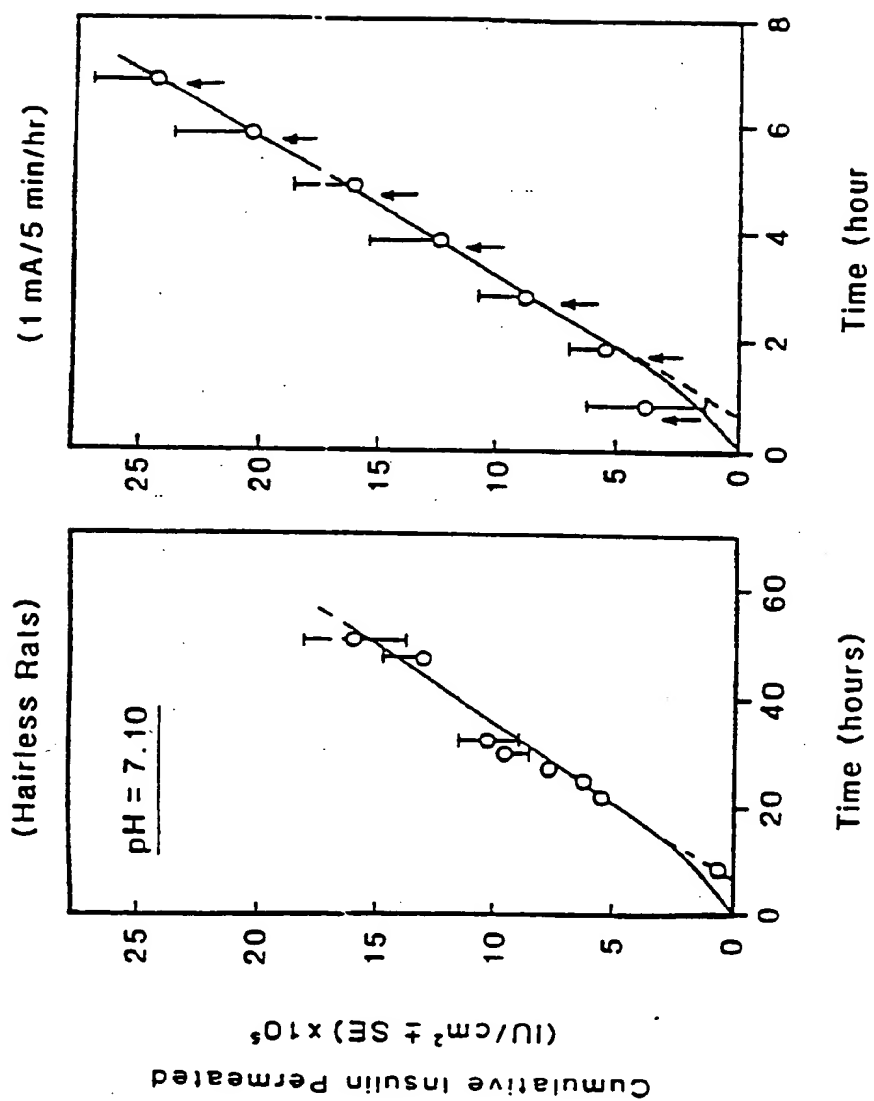


FIG. 22

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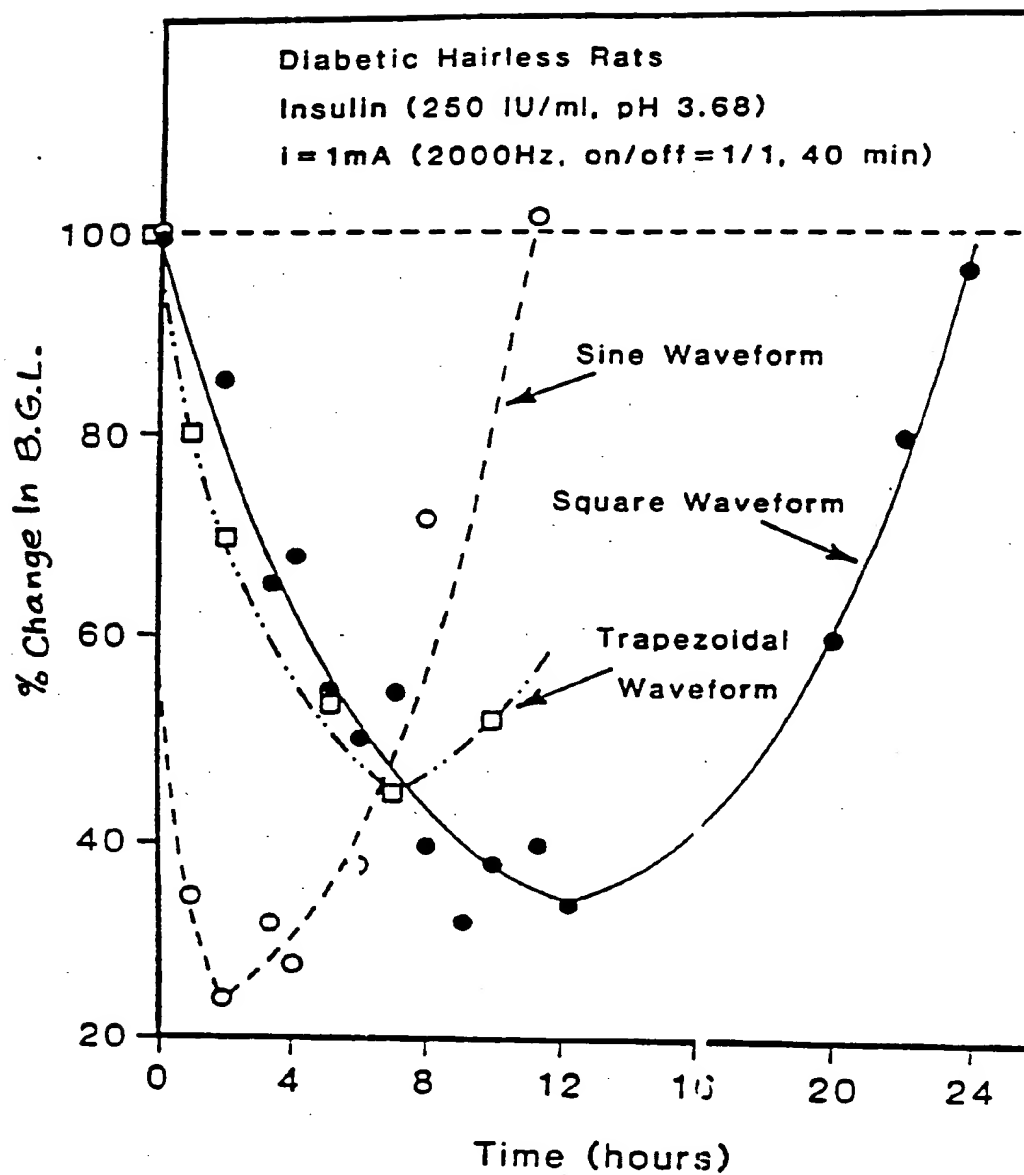


FIG. 24



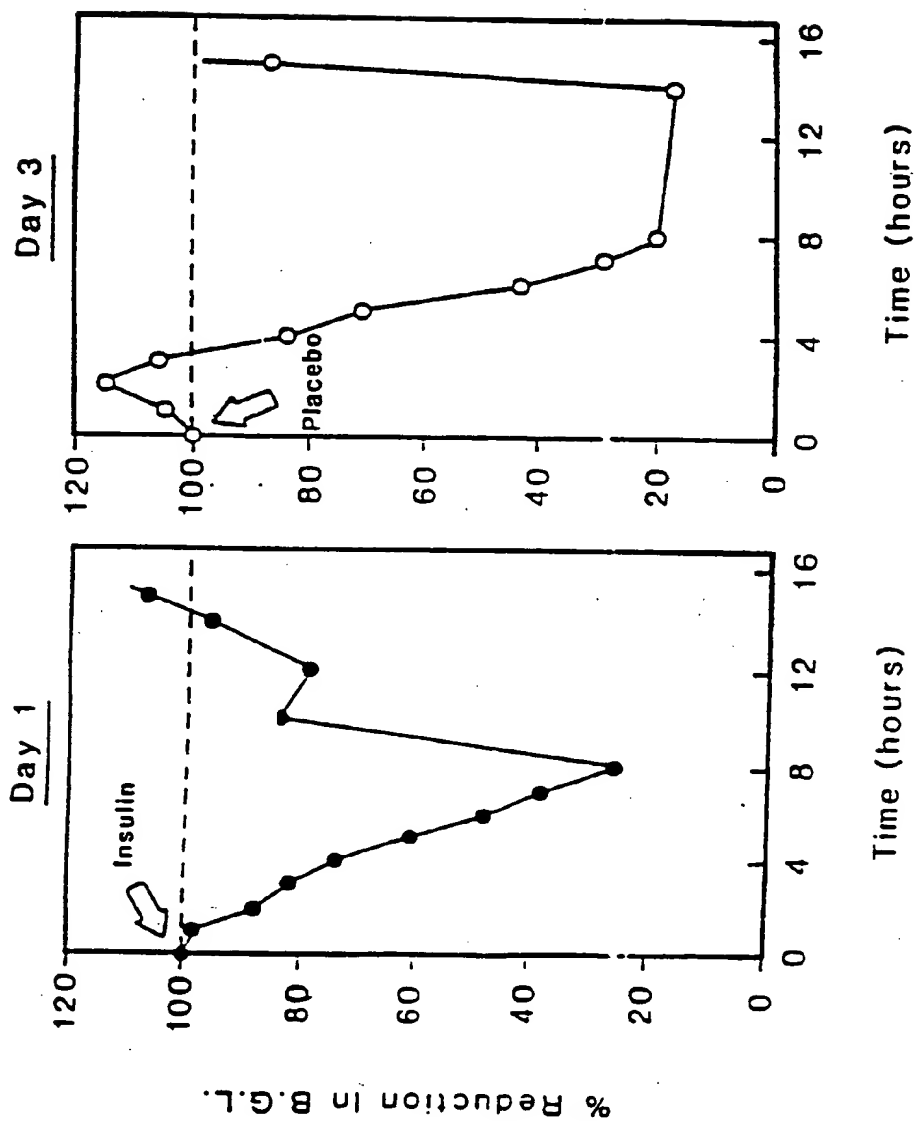
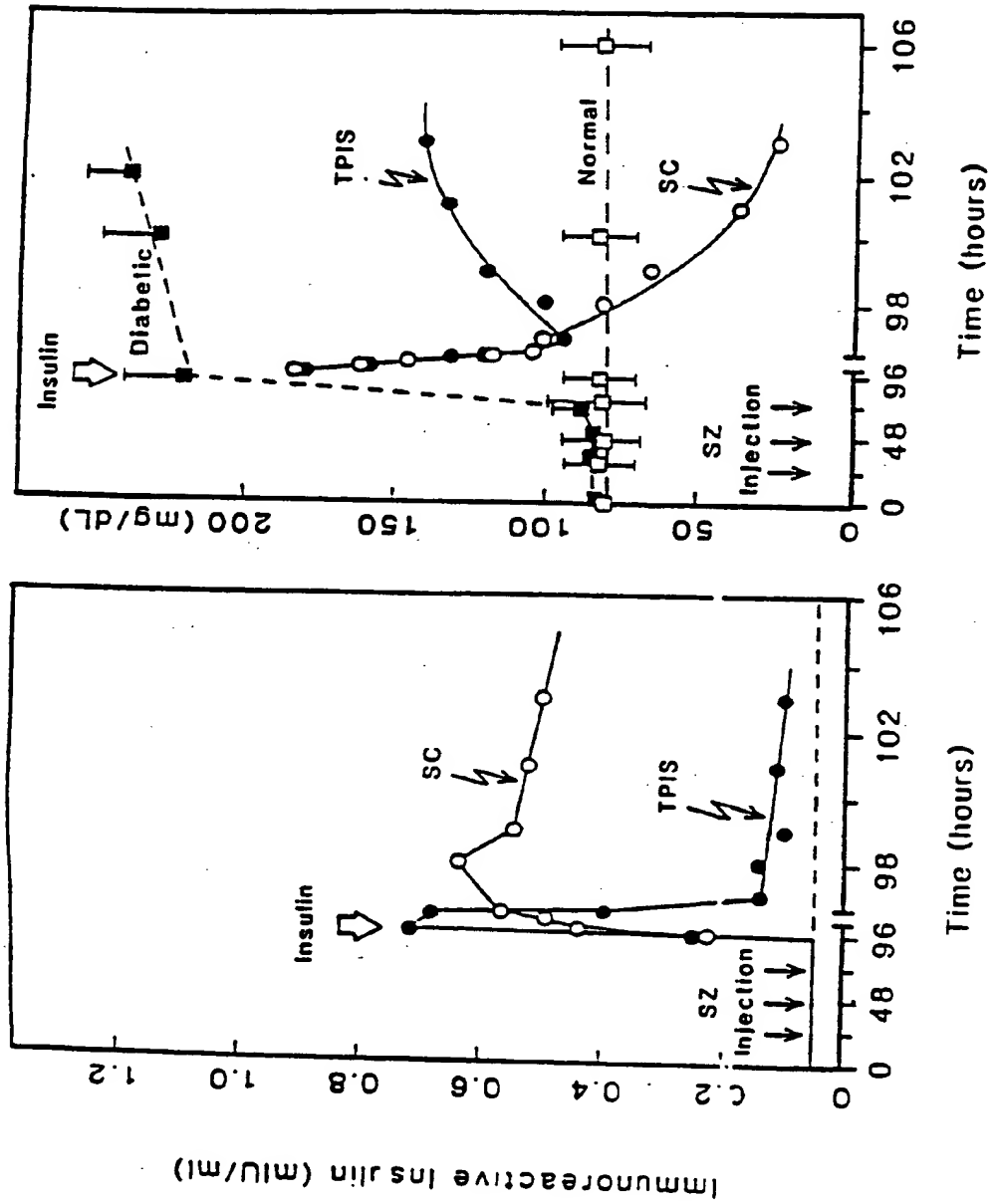


FIG.25B

FIG.25A



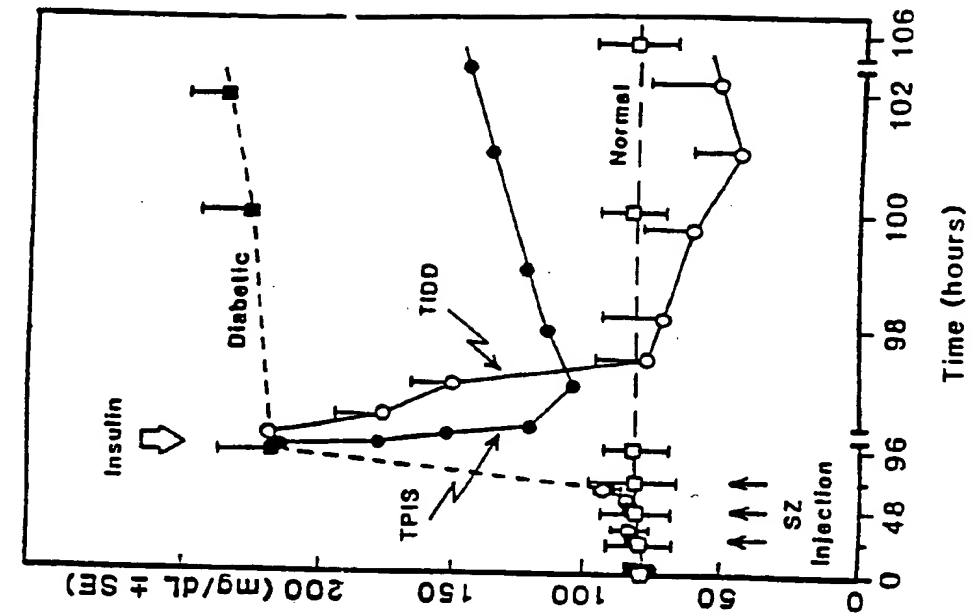


FIG.27B

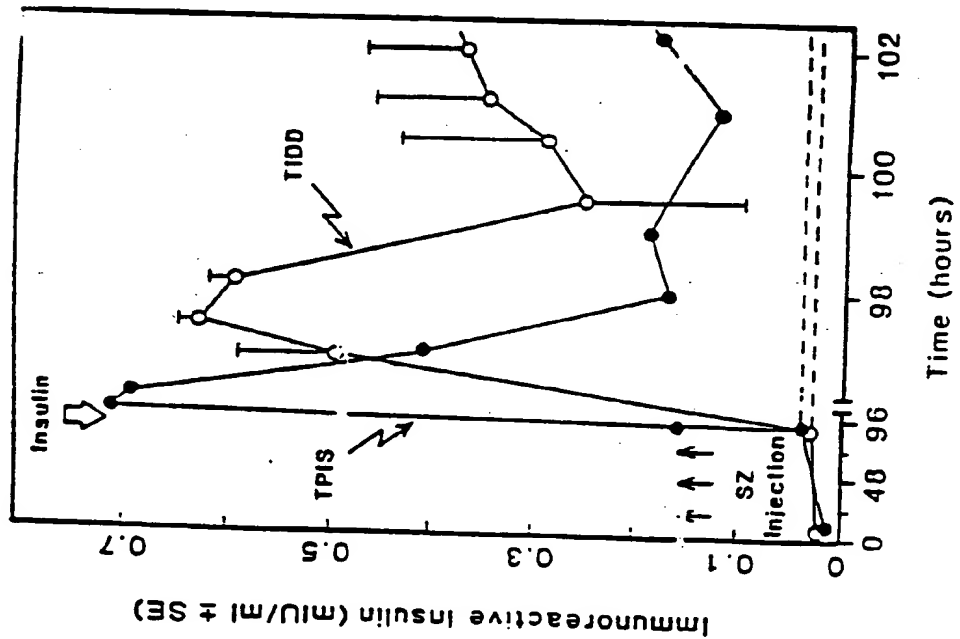


FIG.27A

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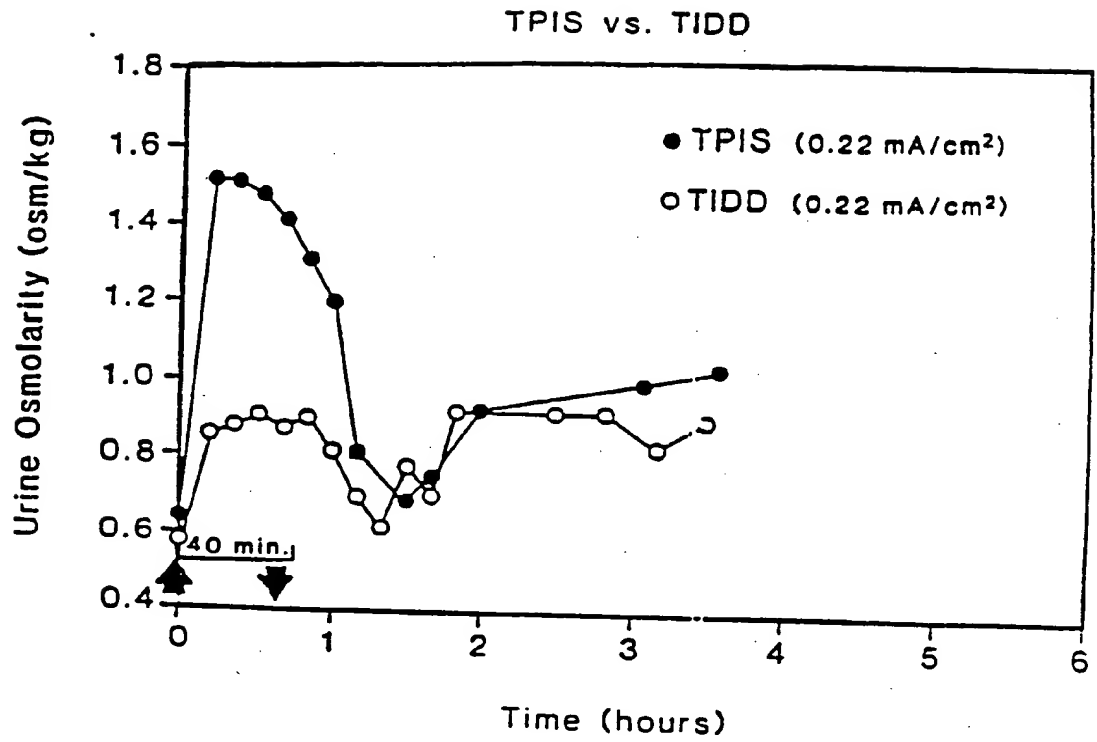


FIG. 28

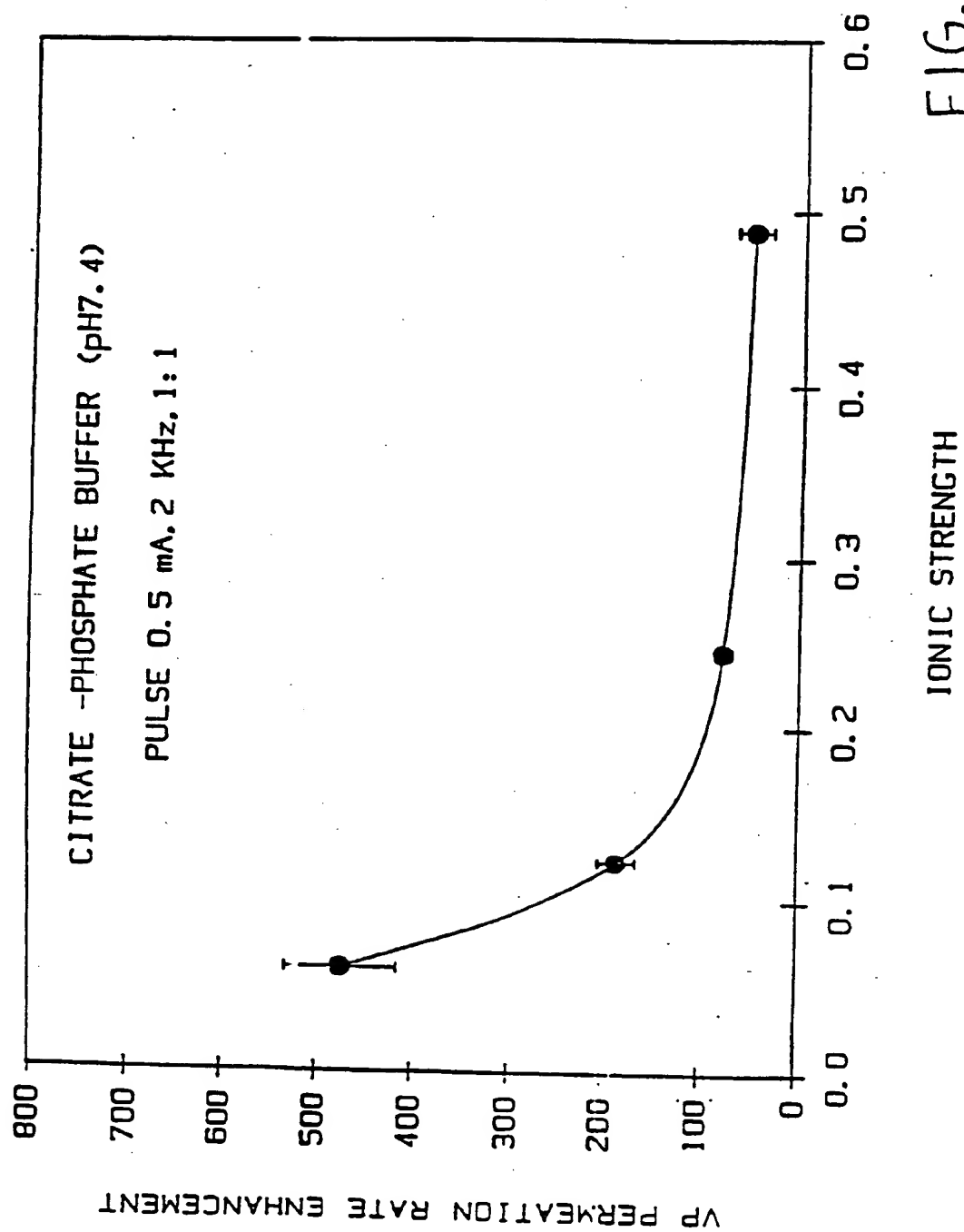


FIG. 29

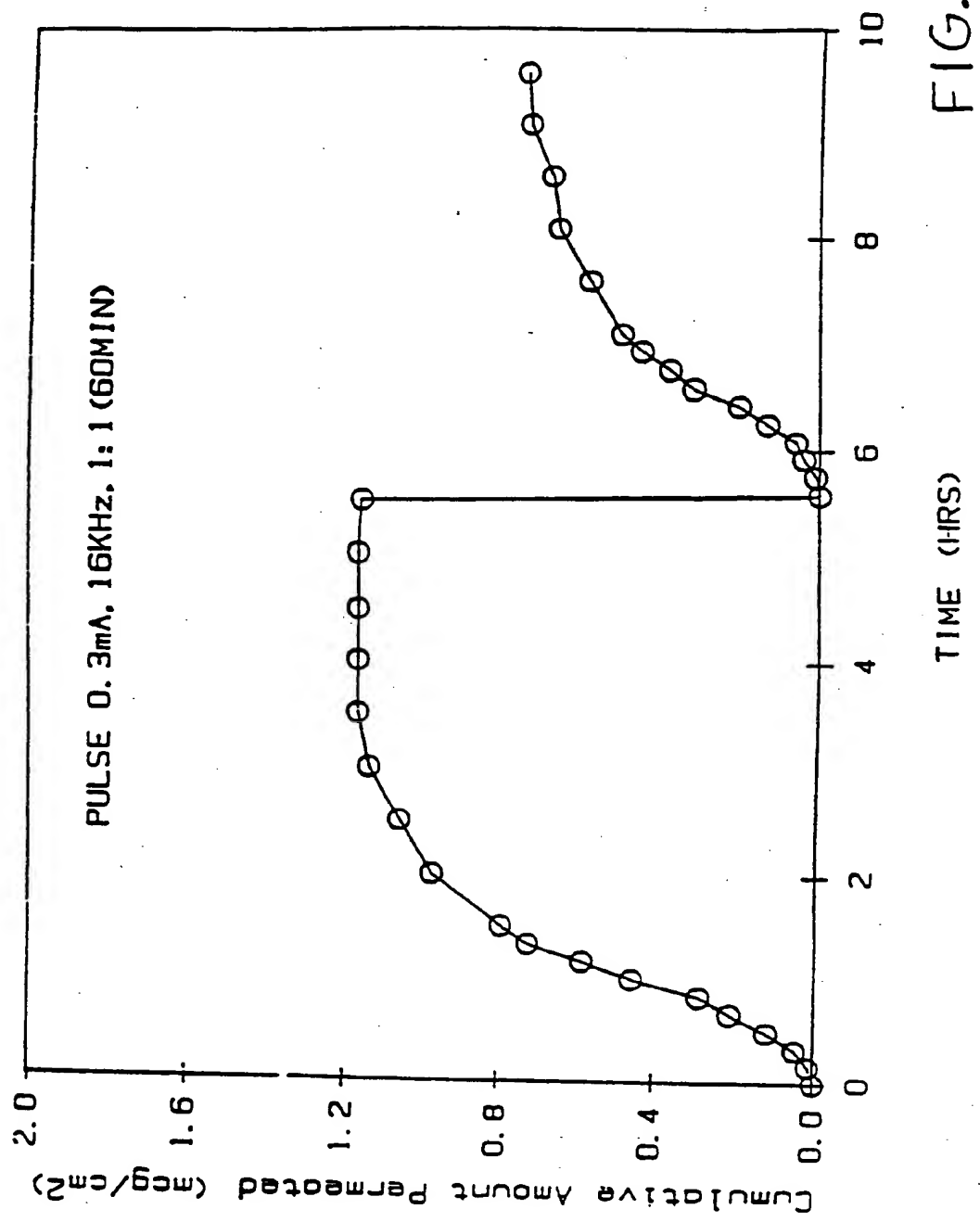


FIG. 30

## INTERNATIONAL SEARCH REPORT

PCT/US92/07221

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :A61N1/30

US CL :604/20

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/748,802,803

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US,A, 5,042,975 (CHEIN ET AL) 27 AUGUST 1991 See entire document	1-19
Y	US,A, 4,722,726 (SANDERSON ET AL) 02 FEBRUARY 1988 See column 7, lines 10-16	1-17
Y	WO,A, 86/07268 (SIBALIS) 18 DECEMBER 1986 See entire document	1-17
A	WO,A, 86/07269 (MCNICHOLS ET AL) 16 FEBRUARY 1988 See Abstract	1-17

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

Special categories of cited documents: *A* document defining the general state of the art which is not considered to be part of particular relevance *E* earlier document published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed		*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *A* document member of the same patent family	
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Date of the actual completion of the international search 23 NOVEMBER 1992	Date of mailing of the international search report JAN 1993
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer MICHAEL RAFA
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-2214

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US92/07221

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,931,046 (NEWMAN) 05 JUNE 1990 See Abstract	1-17
A	US,A, 5,013,293 (SIBALIS) 07 MAY 1991 See entire document	1-17
A	US,A, 5,135,479 (SIBALIS ET AL) 04 AUGUST 1992 See entire document	1-19
A	WO, A, 86/07269 (SIBALIS ET AL.) 18 DECEMBER 1986. See entire document	1-17
A	US,A, 4,942,883 (NEWMAN) 24 JULY 1990. See Abstract, Figures)	1-17